CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 1, Multiple doses, Multicenter, Open-label Study to Evaluate Safety, Tolerability, Immunogenicity and Efficacy of Subcutaneous Injections of PolyPEPI1018 Vaccine as an Add-on Immunotherapy to the Standard-of-Care Maintenance Therapy in Subjects with Metastatic Colorectal Cancer (OBERTO)
Short Protocol Title:	Safety and Immunogenicity of PolyPEPI1018 Vaccine in the Treatment of Metastatic Colorectal Cancer (OBERTO)
Protocol Number:	OBERTO-101 Amendment 3
Name of Investigational Product:	PolyPEPI1018 CRC Vaccine (PolyPEPI1018)
IND Number:	17887 #0001
EudraCT Number:	2017-003850-18
Sponsor:	Treos Bio ZRT Viola utca, 2 8200 Veszprém Hungary
Study Medical Monitor:	Franco Lori, M.D., Ph.D. Chief Medical Officer at Treos Bio ZRT Phone: +39 347 0723942 FAX: +36-1-332-3636 E-mail: franco.lori@treosbio.com
Original Protocol Date:	15 November 2017
Amendment 1 Date	15 January 2018
Amendment 2 Date	August 21 2018
Amendment 3 Date	April 10 2019
Confidentiality Statement:	This document contains information that is the confidential and proprietary property of Treos Bio ZRT. Any use, distribution, or disclosure without the prior written consent of Treos Bio ZRT is strictly prohibited except to the extent required under applicable laws or regulations.
Compliance Statement:	This study will be conducted in accordance with Good Clinical Practice (GCP) as defined in International Conference on Harmonisation (ICH) guidelines and United States (US) Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, and 312, and Title 45 Parts 46, 160, and 164; the International Council for Harmonisation (ICH) document ICH Harmonised Guideline, E6(R2) Integrated Addendum to ICH E6(R1):Guideline for Good Clinical Practice; the European Union (EU) Directives 2001/20/EC and 2005/28/EC; the Declaration of Helsinki (version as currently endorsed by the European Medicines Agency [EMA] and the US Food and Drug Administration [FDA], 1989); Institutional Review Board/Independent Ethics Committee (IRB/IEC) Guidelines; and applicable local legal and regulatory requirements.

CLINICAL STUDY PROTOCOL APPROVAL SIGNATURE PAGE

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Protocol Number:	OBERTO-101
Date of Original Protocol:	15 November 2017
Date of Amendment 1	15 January 2018
Date of Amendment 2	August 21 2018
Date of Amendment 3	April 10 2018

APPROVAL STATEMENT

The undersigned has reviewed the format and content of the above protocol and approved for issuance.

Approved by:

Franco Lori, M.D., Ph.D. Chief Medical Officer	10th April 2019

INVESTIGATOR ACCEPTANCE PAGE

Issue/Date: **15 November 2017**
Date of Amendment 1: **15 January 2018**
Date of Amendment 2: **21 August 2018**
Date of Amendment 3: **10 April 2019**

I have read this protocol for Study OBERTO-101 entitled:

A Phase 1, Multiple doses, Multicenter, Open-label Study to Evaluate Safety, Tolerability, Immunogenicity and Efficacy of Subcutaneous Injections of PolyPEPI1018 Vaccine as an Add-on Immunotherapy to the Standard-of-Care Maintenance Therapy in Subjects with Metastatic Colorectal Cancer (OBERTO)

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing Ethics Committees protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, ICH GCP guidelines, and all applicable national and local regulatory requirements.

Investigator Name (print)

Investigator Signature

Date

SYNOPSIS

Name of Sponsor/Company:	Treos Bio ZRT
Name of Product:	PolyPEPI1018 CRC Vaccine (PolyPEPI1018)
Title of Study:	A Phase 1, Multiple doses, Multicenter, Open-label Study to Evaluate Safety, Tolerability, Immunogenicity and Efficacy of Subcutaneous Injections of PolyPEPI1018 Vaccine as an Add-on Immunotherapy to the Standard-of-Care Maintenance Therapy in Subjects with Metastatic Colorectal Cancer (OBERTO)
Phase of Development:	Phase 1; First-in-Human
Planned Study Period:	Initiation: Second quarter of 2018 (first subject first visit) Primary Completion: Third quarter of 2019 (last subject Week 12 assessment)
Study Objective(s):	Primary Objective: • To evaluate the safety and tolerability of multiple doses of PolyPEPI1018 as an add-on to maintenance therapy in subjects with metastatic colorectal cancer (mCRC) Secondary Objective(s): • To identify PEPIs (Personal EPItopes capable of inducing T cell responses in an individual) from PolyPEPI1018 in each study subject • To evaluate the immunogenicity of PolyPEPI1018 by measuring both effector and memory T cell responses • To evaluate initial efficacy of PolyPEPI1018 by evaluating Objective Response Rate (ORR) Exploratory Objective(s): • To explore the correlation between PEPIs and T cell responses • To explore the correlation between PEPIs and tumor infiltrating lymphocytes • To explore the correlation between T cell responses and tumor infiltrating lymphocytes • To explore the correlation between PEPIs and ORR • To explore the correlation between T cell responses and ORR
Study Design:	This is a Phase 1, open-label, non-randomized, multicenter study to evaluate the safety, tolerability, immunogenicity and efficacy of multiple subcutaneous (SC) injections of PolyPEPI1018 as an add-on immunotherapy to the standard-of-care maintenance therapy in approximately 10 subjects with mCRC. This is an amended Study Design only in the USA: 5 subjects in Italy are under evaluation after a single SC injection of the same vaccine, as originally planned (no amendment contemplated in Italy). The study is composed of a 3-week Screening Period, the administration of multiple doses vaccine (Day 1, Week 0; Day 92, Week 13; Day 183, week 26), a 13-week Follow-up Period between the first and second vaccination and a 12-week Follow-up Period after the last vaccination. The study will be conducted on an outpatient basis. Screening should be performed in parallel with the subject's completion of the standard-of-care first-line treatment and initiation of the standard-of-care maintenance treatment.

	The first dose of PolyPEPI1018 will be administered after the subject initiates the maintenance regimen, and within 3 weeks after the eligibility CT scan was performed (should be performed at the completion of the first-line treatment). Subjects will be monitored every 3 weeks for 12 weeks after first administration of PolyPEPI1018 (i.e. Weeks 3, 6, 9 and 12), then vaccinated again at week 13 and monitored every 3 weeks for 12 weeks after second administration of PolyPEPI1018 (i.e. Weeks 16, 19, 22 and 25), then vaccinated again at week 26 and monitored every 3 weeks for 12 weeks after third administration of PolyPEPI1018 (i.e. Weeks 29, 32, 35 and 38)
Number of Investigational Sites:	Two sites, 1 in the United States (US) and 1 in Europe (Italy)
Planned Number of Subjects:	Approximately 10 subjects in the USA, to be vaccinated 3 times (USA), in addition to 5 subjects to be vaccinate only 1 time (Italy)
Planned Duration of Subject Participation:	Approximately 41 weeks, including a 3-week Screening Period and 12-week Follow-up Period after third and last PolyPEPI1018 dose is administered
Study Population:	Patients with mCRC who have achieved partial response (PR) or stable disease during first-line treatment with chemotherapy plus a biologic drug will be enrolled
Test Product, Dose, and Mode of Administration:	The final dosage form of PolyPEPI1018 is an emulsified solution prepared onsite, by mixing 2 separate solutions of multiple peptides (PolyPEPI1018-Mix1 and PolyPEPI1018-Mix2) and Montanide™ as an adjuvant. The sponsor will provide the following: • PolyPEPI1018-Mix1 - a solution of 2 × 30-mer peptides at 0.2 mg/peptide/mL in 1.5 mL solution (20% DMSO, 80% water) and stored at -20ºC • PolyPEPI1018-Mix2 - a solution of 4 × 30-mer peptides at 0.2 mg/peptide/mL in 1.5 mL solution (20% DMSO, 80% water) and stored at -20ºC The site staff will follow the written vaccine preparation procedure and mix 1.2 mL of PolyPEPI1018-Mix1, 1.2 mL of PolyPEPI1018-Mix2, and 2.4 mL of Montanide™ to produce the emulsified vaccine solution. After preparing the mixture, 1 mL of the mixture must be injected SC into each of 4 selected injection sites (1 mL SC injection per site). After the injections are administered, the subject should be observed for at least 1 hour for any local and/or systemic allergic reactions. Dosage Form: Emulsified solution consisting of PolyPEPI1018-Mix1, PolyPEPI1018-Mix2, and Montanide™ (adjuvant), prepared onsite and used immediately post preparation. Dose Level: 0.2 mg/ peptide, 6 peptides total Mode of Administration: SC injection
Reference Therapy, Dose, and Mode of Administration:	No reference therapy is used in this study
Inclusion Criteria:	1. Male or female subjects, 18-75 years of age at time of Screening who provide written informed consent prior to initiation of any study procedure 2. Histologically confirmed metastatic adenocarcinoma originating from the colon or the rectum

	3. Presence of at least 1 measurable reference lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria 4. Experienced PR or stable disease during first-line treatment with a systemic chemotherapy regimen and 1 biological therapy regimen 5. Maintenance therapy with a fluoropyrimidine (5-fluorouracil or capecitabine) plus the same biologic agent (bevacizumab, cetuximab or panitumumab) used during induction, scheduled to initiate prior to the first day of treatment with the study drug 6. No more than 1 line of chemotherapy regimen for mCRC (adjuvant therapy for non-metastasized disease is allowed if terminated more than 6 months before Screening and without recurrence within 6 months after the end of adjuvant treatment) 7. Last CT scan at 3 weeks or less before the first day of treatment 8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 9. Women of childbearing potential must agree to appropriately use an effective form of contraception (failure rate of <1% per year) for 3 months from the day of the treatment. An effective form of contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or condom 10. Men must agree to use an effective form of contraception (as defined above), and not donate sperm for 3 months from the day of the treatment 11. White blood cell count $\geq 3.0 \times 10^9$/L with neutrophils $\geq 1.5 \times 10^9$/L 12. Platelets $\geq 100 \times 10^9$/L, hemoglobin ≥5.6 mmol/L (corresponding to 9 g/dL) 13. Serum bilirubin ≤1.5 × upper limit of normal (ULN) set by the site 14. Alanine amino transferase (ALAT) and aspartate amino transferase (ASAT) ≤2.5 × ULN in the absence of liver metastases. ALAT and ASAT ≤5 × ULN set by the site in the presence of liver metastases 15. Serum creatinine ≤1.5 × ULN set by the site and creatinine clearance >30 mL/min using Cockroft formula 16. Relevant toxicities of prior therapies must have resolved to ≤Grade 1, except for oxaliplatin-related neuropathy or alopecia 17. Anticipated life expectancy ≥6 months 18. Subject is willing and able to comply with the requirements of the protocol
Exclusion Criteria:	1. Received chronic systemic immune therapy or immunosuppressant medication other than steroids within the last 6 weeks prior to start of study treatment 2. Received continuous systemic steroid treatment within the last 2 weeks prior to start of study treatment 3. Colorectal cancer with documented high microsatellite instability (MSI-H) 4. Colorectal cancer with documented BRAF mutations 5. Pre-existing systemic autoimmune or antibody-mediated diseases or immune deficiency diseases 6. Central nervous system (CNS) metastases 7. Active or uncontrolled severe infections or undiagnosed febrile condition >38ºC

	8. Acute or subacute intestinal obstruction or history of chronic intestinal inflammatory diseases 9. Symptomatic peritoneal carcinomatosis 10. Peritonitis 11. Serious, non-healing wounds, ulcers or bone fractures 12. Nephrotic syndrome 13. Arterial thromboembolisms or severe hemorrhages within 6 months before study enrolment (except bleeding tumor before tumor resection surgery) 14. Hemorrhagic diathesis or thrombotic tendency 15. Major surgery or radiotherapy within 12 weeks prior to the study treatment or anticipation of needing such procedure during the study period 16. Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days 17. Participants with active malignancy (other than colorectal cancer [CRC]) or a prior malignancy within the past 12 months 18. Participant with myocardial infarction within 6 months prior to enrollment or New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to the first dose of study treatment, any electrocardiogram (ECG) abnormality at Screening must be documented by the investigator as not medically relevant 19. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of a live attenuated vaccine will be required during the study 20. Participant has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study 21. Known hypersensitivity to any component of the investigational drug 22. If female, participant is pregnant (exclusion confirmed with beta-human chorionic gonadotropin [hCG] test) or lactating at the time of enrollment, or has plans to become pregnant or start breastfeeding during the study 23. Pre-existing alcohol or drug abuse 24. Medical or mental impairments which make it impossible to obtain the patient's consent or to conduct the study 25. A significant concomitant medical condition which the clinical investigator believes precludes the patient from enrolling in the study 26. Absent or limited legal competence
Primary Endpoint:	Occurrence of at least 1 ≥Grade 4 local adverse event (AE) or 1 ≥Grade 3 systemic AE and/or signs/symptoms, lab toxicities, and/or clinical events that is probably or definitely related to study treatment, any time from Day 1 until 21 days after administration of each dose of the vaccine.
Criteria for Evaluation/Outcome Measures:	<u>Primary Outcome Measures:</u> • The incidence and severity of all adverse events (AEs), related AEs, all serious adverse events (SAEs), related SAEs, and temporally-associated AEs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (v4.0)

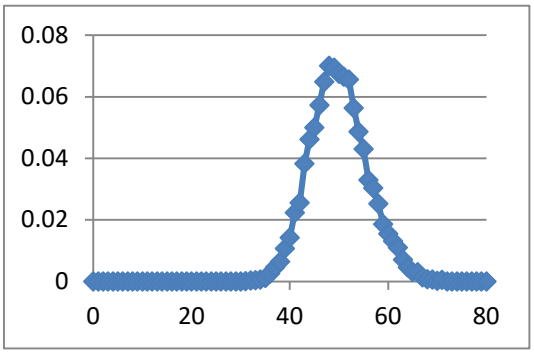
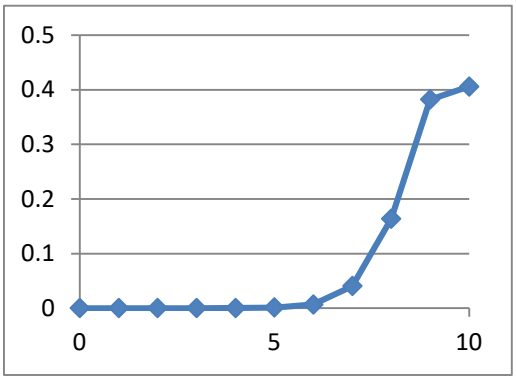
- Change from baseline in clinical laboratory safety parameters and vital signs
- Number and proportion of subjects with any clinically significant change in vital signs (i.e., blood pressure, pulse rate, respiratory rate, body temperature) during the vaccine administration or within 60 minutes following administration

Secondary Outcome Measure(s):

- PEPIs as identified by the PEPI Test
- Effector T cell response against 12 selected epitopes of PolyPEPI1018 as measured by interferon (IFN)-gamma Enzyme-Linked ImmunoSpot (ELISPOT) assay for the following:
  - Number and proportion of subjects with 0, ≥1, ≥2, ≥3, ≥4, ≥5 effector T cell responses, respectively, detected at the Baseline Visits (Week -3 to -1 and Week 0) and at 3, 6-, 9-, and 12-weeks after administration of the vaccine
  - For each subject, the number of effector T cell responses
  - For each subject, the time course of effector T cell response at Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine
- Memory T cell response against 12 selected epitopes of PolyPEPI1018 as measured by the Precursors with High Proliferation Capacity (PHPC) assay for the following:
  - Number and proportion of subjects with 0, ≥1, ≥2, ≥3, ≥4, ≥5 memory T cell response, respectively, detected at the Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine
  - For each subject, the number of positive memory T cell responses
  - For each subject, the time course of memory T cell response at Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine
- Objective Response Rate (ORR) measured by CT scan at Screening Visit (Week -3 to -1), and at 6-, and 12-weeks after administration of each dose of the vaccine

Exploratory Outcome Measures:

- Correlations between PEPIs identified by the PEPI Test and effector and memory T cell responses measured by ELISPOT and PHPC immunogenicity assays
- Change in relative counts of tumor infiltrating lymphocytes (TILs) in accessible tumor biopsies at Baseline (Week -3 to -1) and at Week 12 as measured by immunohistochemistry
- Correlation between PEPIs identified by the PEPI Test and infiltrating lymphocyte in tumor biopsies measured by immunohistochemistry
- Correlations between T cell responses measured by ELISPOT and PHPC and infiltrating lymphocyte in tumor biopsies measured by immunohistochemistry
- Correlations between PEPIs identified by the PEPI Test and effector and ORR
- Correlations between T cell responses measured by ELISPOT and PHPC and ORR

Sample Size Justification:	Approximately 10 subjects will be enrolled in the study to receive three vaccinations. The study is not statistically powered to assess the primary or secondary outcomes measures. Assuming that the human leukocyte antigen (HLA) sets from the subjects follow the distribution observed in the HLA sets from the in-house database, at least 39 positive immune responses are expected from 10 subjects. The distribution of the expected number of positive tests is displayed in Figure S1, which is generated from 10,000 simulations. The x-axis shows the number of positive tests, and the y-axis shows the probabilities. **Figure S1. Distribution of the Expected Number of Positive Tests**  Based on the simulation, at least 7 subjects are expected to have an immune response against 2 or more cancer antigens with at least 97.5% probability. The expected distribution of probabilities having a given number of subjects with positive immune response for 2 or more antigens is displayed in Figure S2, the x-axis shows the number of subjects with a given probability and the y-axis shows the probability. **Figures S2. Expected Distribution of Probabilities Having a Given Number of Subjects with Positive Immune Response for Two or More Antigens** 
Statistical Methods and Analyses:	Demographic and baseline characteristics will be summarized using descriptive statistics. Safety/tolerability will be assessed by tabulating the number and percentage of subjects who develop 1 or more related Grade 3 or higher systemic SAEs and/or Grade 4 or higher local SAEs. The incidence of AEs, the incidence of treatment-related AEs, and the severity of AEs will be summarized using descriptive statistics. Other safety parameters (injection site reactions, clinical laboratory parameters, vital signs, ECG measures) and the change from Baseline in these parameters will be summarized using descriptive statistics.

	Immunogenicity parameters versus time will be plotted for each subject; similar summary plots will be constructed for the 10 subjects. Efficacy parameters versus time will be plotted for each subject; similar summary plots will be constructed for the 10 subjects. Correlation and significance tests will be performed on the results of exploratory measures.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALAT	alanine amino transferase
ASAT	aspartate amino transferase
CA 19-9	cancer antigen
CDx	companion diagnostic
CEA	carcinoembryonic antigen
CNS	central nervous system
CPI	checkpoint inhibitors
CRC	colorectal cancer
CRF	case report form
CTA	cancer testis antigen
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T lymphocyte
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISPOT	Enzyme-Linked ImmunoSpot
EU	European Union
5FU	5-fluorouracil
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
HLA	human leukocyte antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IFN	interferon
IHC	immunohistochemistry
IP	investigational product
IRB	Institutional Review Boards
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities

MEK	MAPK/ERK kinase
MSI-H	high microsatellite instability
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NMC	non-medical complaint
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PEPI	personal epitope
PHPC	Precursors with High Proliferation Capacity
PR	partial response
RAS	Rat Sarcoma Viral Oncogene Homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference Safety Information
SAE	serious adverse event
SAER	SAE report
SAS	Safety Analysis Set
SC	subcutaneous(ly)
SIC	subject identification code
SoA	Schedule of Study Assessments
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
ULN	upper limit of normal
US	United States
WT	wildtype

1 BACKGROUND INFORMATION

1.1 Colorectal Cancer Background

Colorectal cancer is a leading cause of cancer-related mortality worldwide. In the European Union (EU-28) and the World Health Organization Europe Region, the mean mortality rates per 100,000 population are respectively 15.2 and 15.7 for men and 9.0 and 9.7 for women (Ferlay 2015). The mean incidence rate of colorectal cancer in the EU-28 is 31.3 per 100,000 population (39.5 per 100,000 population for men and 24.4 per 100,000 population for women), with 345,000 new cases per year.

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in men and women in the United States (US). In 2010, the US spent $14 billion for the management of colorectal cancer (Mariotto 2011).

While multidisciplinary care is employed in the treatment of localized colon cancer, systemic chemotherapy is the mainstay of treatment in metastatic colorectal cancer (mCRC). There are currently 10 Food and Drug Administration (FDA) approved drugs for the management of mCRC, including 5-fluorouracil (5FU), oxaliplatin, irinotecan, capecitabine, bevacizumab, cetuximab, panitumumab, ziv- aflibercept, regorafenib and ramucirumab. There are a variety of regimens with different combinations of these drugs, for use in first-, second-, and third-line settings of treatment. For example, 5FU, oxaliplatin (FOLFOX) and bevacizumab are commonly used as a first-line therapy (Saltz 2008). The Rat Sarcoma Viral Oncogene Homolog (RAS) is a family of genes including KRAS and NRAS that are often found to be mutated in colorectal cancer. When a tumor is RAS wildtype (WT), patients derive benefit from monoclonal antibodies, such as cetuximab or panitumumab, which target the epidermal growth factor receptor (EGFR). Thus, EGFR targeted therapy, in addition to chemotherapy, is a common second-line strategy for patients with RAS WT disease (Seymour 2013). The chemotherapy backbone used in second-line treatment is often 5FU and irinotecan (FOLFIRI), with regorafenib monotherapy commonly used as a third-line option (Grothey 2013). More recently it has been shown that FOLFOXIRI plus bevacizumab compared with FOLFIRI plus bevacizumab, improve the outcome in patients with mCRC (Loupakis 2014).

Despite the available treatment options, response rates to mCRC remain low. Multiple therapies with novel mechanisms of actions are being developed to treat mCRC, including small molecule tyrosine kinase inhibitors, and MAPK/ERK kinase (MEK; also known as MAP2K) inhibitors. BRAF mutations, usually associated with poor prognosis, are found in ~10% of patients with colorectal cancer (CRC), and small molecule inhibitors of BRAF are being developed as combination treatments with other available therapies (Cassidy 2017).

Immunotherapy is an attractive treatment option since it is more tolerable than conventional chemotherapy with potential long-lasting durable responses. Novel checkpoint inhibitors (CPIs) have demonstrated unprecedented clinical activity in a wide range of cancers. The observation of clinical activity in microsatellite instability-high (MSI-H) mCRC was the first indication of a potential for mCRC to respond to these agents, and has led to a breakthrough designation by the FDA for CPI use in this subset of patients (estimated as 5% to 10% of the patient population with mCRC). However, a proportion of MSI-H, and nearly all microsatellite stable disease, does not respond to single-agent checkpoint inhibition, and clinical trials are ongoing to increase responses to immunotherapy in mCRC through both better patient selection and novel combinations of immunotherapeutic agents (Bever 2017).

1.2 PolyPEPI1018 and Companion Diagnostic Vaccine Overview

PolyPEPI1018 CRC Vaccine (PolyPEPI1018) and companion diagnostic (CDx) product is a precision CRC vaccine that takes into account an individual patient's genetics and tumor heterogeneities using information technology during product design and responder selection processes. The subcutaneously (SC) injected vaccine product is a mixture of 6 synthetic peptides (Table 1) and the adjuvant Montanide™.

The CDx is a pharmacogenetic test to be co-developed with PolyPEPI1018, which will select patients who most likely respond to vaccine treatment. The CDx uses the complete human leukocyte antigen (HLA) genotype of the patient for the identification of personal epitopes (PEPIs) that induce T Cell responses. To identify PEPIs the sponsor developed the novel PEPI Test. As described in Section 6.6.1, the PEPI Test selects, from HLA restricted epitopes, certain PEPIs that are capable of activating T cells in an individual. PEPIs are genetic biomarkers specific to the HLA genotype of an individual patient. The

PolyPEPI10108 CDx will use the PEPI Test to identify the patient's PEPIs from PolyPEPI1018. Data from a retrospective correlation study performed by the sponsor suggest that patients with PEPIs derived from multiple CRC antigens are likely to benefit from PolyPEPI1018 vaccination.

Table 1. Synthetic Peptide Sequences

ID	Sequence
CRC_P1	PSTTMETQFPVSEGKSRYRAQRFWSWVGQA
CRC_P2	VRTYWIIIELKHKARTAKKVRRAIEQLAAM
CRC_P3	YVDEKAPEFSMQGLKDEKVAELVRFLLRKY
CRC_P6	PKSMTMMPALFKENRSGAVMSERVSGLAGS
CRC_P7	KFMNPYNAVLTKKFQKVNFFFERIMKYERL
CRC_P8	AQKMSSLLPTMWLGAFKKTMSTFHNLVSLN

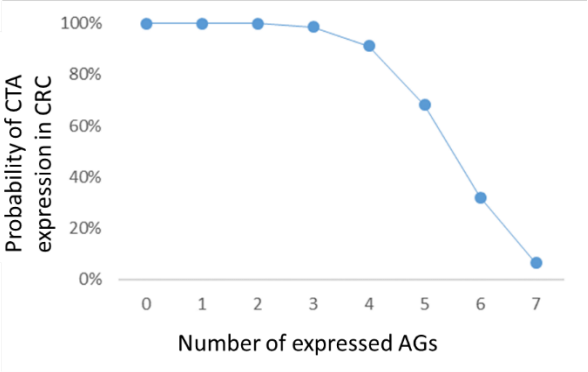
The 6 peptides in PolyPEPI1018 contain 12 novel and distinct selected epitopes which are derived from 7 conserved cancer testis antigens (CTAs) that act in combination to activate T cells against CRC antigens in a high proportion of patients.

The 7 most frequently expressed CTAs in CRC were selected as targets of PolyPEPI1018, and statistical analysis demonstrates a 95% probability that 3 of these 7 CTAs are expressed in any CRC cell (Figure 1). Given the high probability of targeting CRC expressed CTAs by PolyPEPI1018, tumor biopsy and CTA expression analysis, a risky, inaccurate and costly procedure[1], is not required prior to vaccination with PolyPEPI1018.

[1] There is no validated diagnostic device available to perform tumor antigen expression profiling from tumor biopsies. In addition, a biopsy does not comprehensively characterize a heterogeneous tumor, especially in the metastatic stage.

Figure 1. Cancer Testis Antigens Targeted by PolyPEPI1018

CTA	Expression rate in CRC (2,391 experiment)
TSP50	89.47%
EpCAM	88.35%
Survivin	87.28%
CAGE1	74.47%
SPAG9	74.36%
FBXO39	38.60%
MAGE-A8	43.75%



Abbreviations: CRC = colorectal cancer; CTA = cancer testis antigen

Left: Expression rate in CRC obtained from 2,391 CTA expression analyses in tumor specimens.

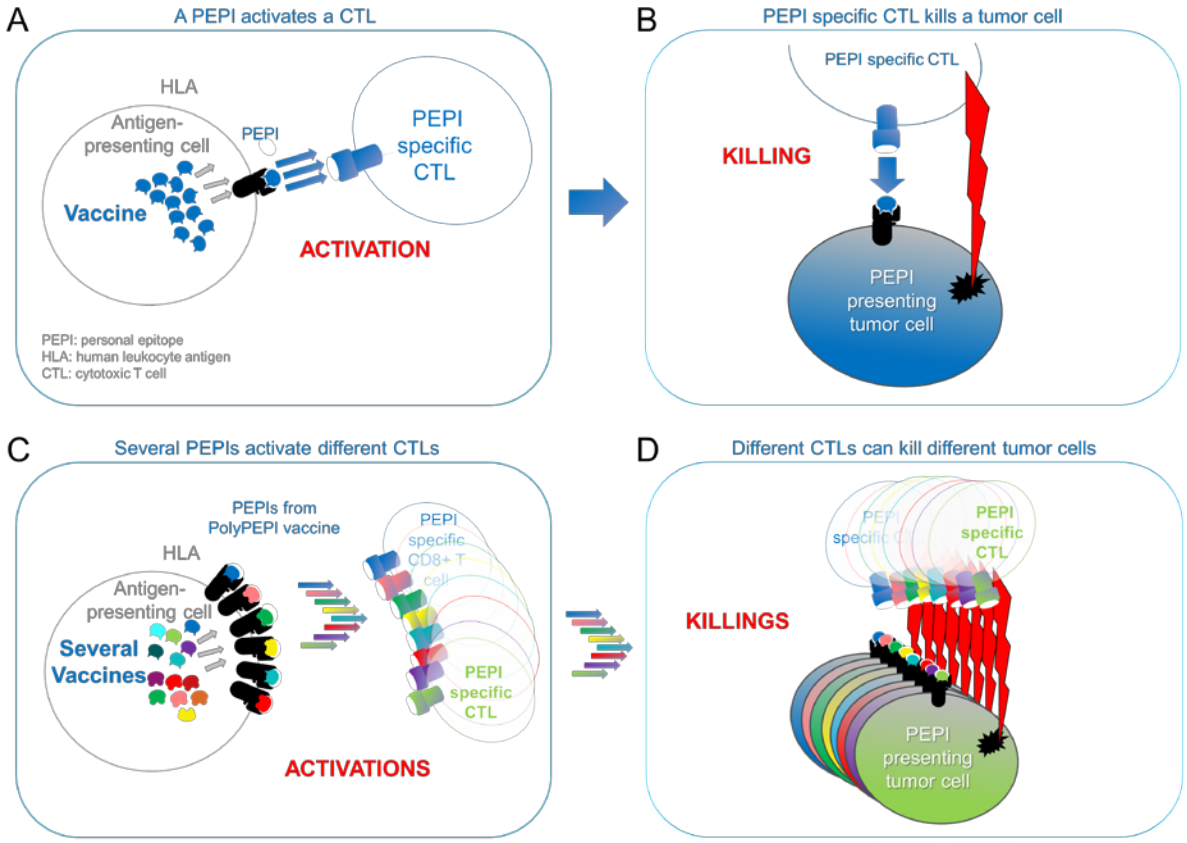
Right: Probability of expression in CRC tumor shows that 3 out of 7 CTAs are expressed in each tumor with >95% probability.

1.2.1 Mechanism of Action

Cancer vaccines represent the next generation immunotherapies (Chen 2013). They induce specific immune responses against tumor antigens, thereby boosting the immune system to attack cells expressing the targeted antigens. Tumor antigens that are currently being targeted by available immunotherapies include MUC1 and NY-ESO-1. Though current cancer vaccines have an excellent safety profile, the response rate is low due to poor antigen selection and the absence of a biomarker for identification of likely responders.

PolyPEPI1018 induces PEPI-specific immune responses against multiple CTAs that are expressed in CRC and are not typically expressed beyond embryonic development in healthy cells. One PEPI derived from one tumor antigen can activate one cytotoxic T lymphocyte (CTL) to proliferate (clonal expansion) and kill tumor cells that present the same PEPI. If the patient has a homogenous tumor that consists of a single type of cell which presents the same PEPI, treatment with a single peptide vaccine could be successful. However, most tumors, especially at the metastatic stage, represent a fast-evolving group of heterogeneous tumor cells which differ in antigen expression and PEPI presentation. Therefore, boosting several CTL clones (i.e., polyvalent immune responses) using a combination of vaccines increases the probability of tumor cell recognition and tumor killing (Figure 2).

Figure 2. Mechanism of Action of Precision PolyPEPI1018 CRC Vaccine



Abbreviations: CTL = cytotoxic T lymphocyte; HLA = human leukocyte antigen; PEPI = personal epitope

A: One peptide in the vaccine is processed to PEPI in the body of the patient by antigen presenting cells (APC). The patient's HLA molecules on the APC bind and present the PEPI to activate a CTL. This CTL proliferates and differentiates to a PEPI-specific CTL.

B: A PEPI-specific CTL is able to recognize and destroy the tumor cells presenting the same PEPI.

C: PolyPEPI1018 is based on the combination of several vaccines capable to induce multiple different PEPI-specific CTLs.

D: These CTLs may recognize and destroy heterologous tumor cells in the patient presenting the same PEPIs.

1.2.2 Preclinical and Clinical Background for PolyPEPI1018

PolyPEPI1018 will be evaluated in patients with mCRC. Since this is a first-in-human study, clinical safety and efficacy data from other peptide vaccines are summarized in the sections below.

1.2.2.1 Safety of Peptide Vaccines and Montanide™

Overall there is a well-established safety profile for peptide vaccines and the adjuvant Montanide™. To date, there are 22 published clinical trials, in 813 patients, on peptide

vaccines formulated with the adjuvant Montanide™ (details are provided in the Investigator Brochure).

The most common side effect of peptide vaccines is inflammation at the injection site, including redness, pain, swelling, warming of the skin, itchiness, and rash. Occasionally, but rarely, unacceptable local skin reactions developed after 10 or more vaccinations, causing treatment to be terminated. After receiving a peptide vaccine, patients occasionally experienced flu-like symptoms, including fever, chills, weakness, dizziness, nausea or vomiting, muscle ache, fatigue, headache, and occasional breathing difficulties. Blood pressure was also affected in some subjects who received a peptide vaccine. Many of these side effects, which last for a short time, are signs/symptoms of inflammation (similar to those occurring after an acute viral infection), likely indicating that the patient was mounting an immune response.

Peptide vaccines, like any other medication affecting the immune system, can cause adverse effects that may prove life threatening. For example, severe hypersensitivity (allergic) reactions to specific vaccine ingredients have occurred following vaccination; however, such severe reactions are very rare (Yoshida 2011). Furthermore, the design of PolyPEPI1018 excludes peptides containing self-epitopes, thus reducing to a minimum the risk of autoimmune and/or hypersensitivity reactions.

In the 813 subjects from the 22 published clinical trials on peptide vaccines formulated with Montanide™ the most serious adverse events (SAEs) were caused by cancer progression. Vaccine-related Grade 3 events were very rare (6 events, 0.7%), and consisted of skin reactions or cellulitis at the injection site, edemas of the head and neck regions, colitis, rectal bleeding and bladder-vaginal fistulae.

1.2.2.2 Efficacy of Peptide Vaccines

PolyPEPI1018 belongs to the class of peptide vaccines. Previous clinical studies have demonstrated that peptide vaccines induce CTL responses. However, the main limitation of these peptide vaccines is the absence of the induction of CTL responses against multiple antigens expressed in tumor cells.

The sponsor hypothesized that induction of antigen specific immune response against multiple antigens that are expressed by the tumor cells will substantially improve the immune response rate and efficacy of the cancer vaccine. Consistent with this expectation, preliminary clinical results with IMA901 peptide vaccines demonstrated that polyvalent tumor specific CTL responses led to clinical benefit in renal cancer patients (Walter 2012); two independent studies with personalized cancer vaccines confirmed these findings in melanoma patients (Ott 2017; Sahin 2017).

A retrospective clinical study conducted by the sponsor demonstrated significant correlation between objective response rate (ORR) of cancer vaccines containing multiple antigens and PEPIs on at least 2 vaccine antigens (see the Investigator Brochure). These data suggest that that patients with PEPIs derived from multiple CRC antigens are likely to benefit from PolyPEPI1018 vaccinations.

1.3 Rationale for Study Design and Dose Regimen

Treos Bio ZRT (sponsor) has developed a vaccine, PolyPEPI1018, which has the potential to elicit an immune response in most individuals with mCRC. Such an immune response is expected to control, reduce, or eliminate cancer in those patients.

The sponsor elected to move from a single vaccination (as originally planned) to multiple (N=3) vaccinations during this first-in-human study to establish the rate, intensity, and evolution of immune responses to PolyPEPI1018 as well as initial efficacy. Since a sufficient time (typically 3 months/12 weeks) is required after vaccination to observe the time course of both effector and memory T cell responses, the maintenance phase following first-line therapy of mCRC (a 4 to 6 month period when the tumor, therapy, and patient's condition are expected to remain stable [Heinemann 2014; Cremolini 2015; Venook 2017]) is the preferred period for treatment with PolyPEPI1018 since it offers optimal conditions for monitoring the time course of immune response after at least the initial vaccination. If a progression occurs during the course of the trial the subject will still be immunized at the expected times (Weeks 13 and 26), even when a second line therapy is needed and administered.

Understanding the evolution of T cell response after vaccination will provide valuable information to design the vaccine administration schedule in future clinical studies.

Moreover, a clean readout of immune responses after single vaccination with adequate follow-up will allow a better assessment of whether the PEPI Test can accurately predict immune responses. Clarifying such correlation will provide a predictive tool that can be used as a CDx in future trials. Therefore, multiple vaccinations 13 week apart with a 12-week follow-up period after third and final vaccination will provide information to design subsequent Phase 2/3 trials.

Only 1 line of prior mCRC chemotherapy treatment is allowed for subjects in this study since response to second- and third-line therapy is often associated with worse and shorter response compared with first-line therapy. Therefore, allowing more than 1 line of prior chemotherapy would not fulfil the expectation of stable conditions during the 12-week follow-up period after first vaccination.

Male or female subjects must be between 18 years and 75 years of age at time of Screening since a robust immune system is needed to elicit an appropriate immune response to vaccination with PolyPEPI1018. Also for this reason, subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The sponsor intends to explore whether multiple vaccinations are able to elicit an immune response that is sufficiently robust to generate tumor infiltrating lymphocytes (Klintrup 2005), and whether this correlates with PEPIs. The sponsor also intends to explore the initial efficacy of PolyPEPI1018 multiple vaccinations. Consequently, subjects must have histologically confirmed metastatic adenocarcinoma originating from the colon or the rectum, with the presence of at least 1 measurable reference lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

The progression of CRC during the 12 weeks following each vaccination will be monitored by CT scan every 6 weeks not only to measure efficacy but also to establish whether subject need to start a second line induction therapy.

Subjects in the study will receive maintenance therapy with a fluoropyrimidine (5-fluorouracil or capecitabine) plus the same biologic agent (bevacizumab, cetuximab or panitumumab) used during induction. It is typically assumed that chemotherapy is immune

suppressive; however, recent advances have shown that in several instances chemotherapy might exert positive effects on immune responses by inducing mechanisms that potentiate immunity (Emens 2015). It is also anticipated that treatment with a biologic drug during maintenance therapy will not interfere with vaccination. Studies have shown that EGFR inhibitors do not interfere with immunotherapies and bevacizumab potentiates immune responses (Terme 2013; Mansfield 2013). Therefore, subjects will be immunized even when a second line therapy is administered.

Finally, maintenance therapy is allowed with 1 biological therapy regimen with or without a systemic chemotherapy regimen scheduled to initiate prior to vaccination and to continue throughout the 12-week follow-up period. Thus, patients may receive standard-of-care treatment while participating in this study, including introducing a second line therapy, if needed.

1.4 Benefits and Risks

It is expected that PolyPEPI1018 will induce PEPI-specific immune responses against multiple CTAs expressed in CRC cells. Previous clinical studies have demonstrated that peptide vaccines similar to PolyPEPI1018 induce CTL responses. Recently, 2 independent studies have shown that personalized vaccination of melanoma patients, with selected mutant proteins identified as being the most likely to generate an immune response, resulted in atypically long relapse-free durations after vaccination (Ott 2017; Sahin 2017).

Limitations of most vaccines include a lengthy period needed to identify the targets, formulate and manufacture vaccines. The present study would provide information for vaccine improvement. As described in Section 1.2, PolyPEPI1018 consists of the 7 most frequently expressed CTAs in CRC, and there is a 95% probability the 3 of these 7 CTAs are expressed in any CRC cell. It is expected that PolyPEPI1018 will induce cytotoxic T cell responses against CTAs expressed in CRC cells, thereby matching the vaccines to patient's tumor antigens and whole HLA genotype. Only a saliva sample, not the traditionally required tumor biopsy, will be required for performing the PEPI Test for the identification of likely responders, thus simplifying and accelerating the selection procedure.

In order to examine whether the PEPI Test can predict immune responses and identify potential responders (thus providing the basis and the rationale for its use as CDx in future studies) it is essential that the present study allows 12 weeks of follow-up after each vaccination. This will also provide useful information to inform us on scheduling (how often vaccination should be repeated) during future multiple-vaccination studies.

As described in Section 1.2.2.1, based on the safety profile of similar vaccines, PolyPEPI1018 is expected to be safe and well-tolerated. Side effects are typically mild (Section 1.2.2.1.). Local erythema and edema in the site of vaccination are expected, as well as a flu-like syndrome with minor fever and fatigue. Vaccines, like any other medication that affects the immune system, can cause adverse effects that may prove life threatening. For example, severe hypersensitivity (allergic) reactions to specific vaccine ingredients have occurred following vaccination; however, such severe reactions are very rare (Yoshida 2011). Furthermore, the design of PolyPEPI1018 excludes peptides containing self-epitopes, thus reducing the risk of autoimmune and/or hypersensitivity reactions to a minimum.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is:

- To evaluate the safety and tolerability of a multiple doses of PolyPEPI1018 as an add-on to maintenance therapy in subjects with metastatic colorectal cancer (mCRC)

2.2 Secondary Objectives

The secondary objectives of this study are:

- To identify PEPIs (Personal EPItopes capable of inducing T cell responses in an individual) from PolyPEPI1018 in each study subject
- To evaluate the immunogenicity of PolyPEPI1018 by measuring both effector and memory T cell responses
- To evaluate initial efficacy of PolyPEPI1018 by evaluating Objective Response Rate (ORR)

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the correlation between PEPIs and T cell responses
- To explore the correlation between PEPIs and tumor infiltrating lymphocytes
- To explore the correlation between T cell responses and tumor infiltrating lymphocytes
- To explore the correlation between PEPIs and ORR
- To explore the correlation between T cell responses and ORR

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 1, open-label, non-randomized, multicenter study to evaluate the safety, tolerability, immunogenicity and efficacy of multiple subcutaneous (SC) injections of PolyPEPI1018 as an add-on immunotherapy to the standard-of-care maintenance therapy in approximately 10 subjects with mCRC. This is an amended Study Design only in the USA: 5 subjects in Italy are under evaluation after only a single SC injection of the same vaccine, as originally planned.

The study is composed of a 3-week Screening Period, the administration of multiple doses vaccine (Day 1, Week 0; Day 92, Week 13; Day 183, week 26), a 13-week Follow-up Period between the first and second vaccination and a 12-week Follow-up Period after the last vaccination. The study will be conducted on an outpatient basis.

The Screening Period will occur between 21 days and 1 day prior to administration of PolyPEPI1018 administration. Screening should be performed in parallel with the subject's completion of the standard-of-care first-line treatment and initiation of the standard-of-care maintenance treatment. During this study period, results from a CT scan, which should be performed at the completion of the first-line treatment regimen, must be obtained. The results from the CT scan must confirm that the subject has responded to first-line chemotherapy with documentation of cancer regression or lack of progression, according to the RECIST version 1.1 criteria. Once informed consent has been obtained, the subject will undergo a biopsy procedure in one of the accessible tumors (primary or metastasis) to check for tumor infiltrating lymphocytes (TILs).

The first dose of PolyPEPI1018 will be administered on Day 1 of Week 0 and must be (1) after the subject initiates the maintenance regimen, and (2) within 3 weeks after the eligibility CT scan was performed. Vaccination will be performed at 4 anatomic sites (preferably draining to axillary or inguinal lymph nodes) and administered by SC injection. After the last injection, the subject must remain at the site for at least 1 hour to be monitored for any local and/or systemic allergic reactions. A buccal swab will be collected to determine

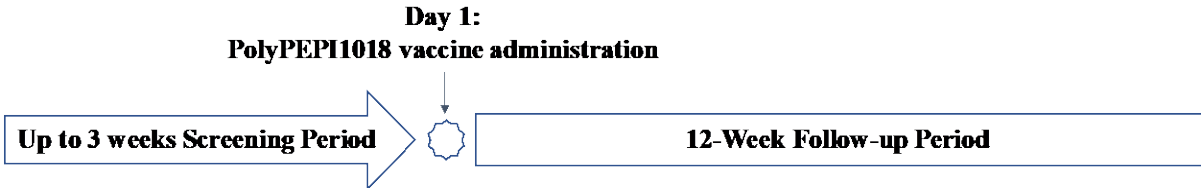
HLA types. A subject diary will be distributed to subjects to collect local signs related to the injection sites, physical fatigue, and body temperature.

Subjects will be monitored every 3 weeks for 12 weeks after first administration of PolyPEPI1018 (i.e. Weeks 3, 6, 9 and 12), then vaccinated again at week 13 and monitored every 3 weeks for 12 weeks after second administration of PolyPEPI1018 (i.e. Weeks 16, 19, 22 and 25), then vaccinated again at week 26 and monitored every 3 weeks for 12 weeks after third administration of PolyPEPI1018 (i.e. Weeks 29, 32, 35 and 38).

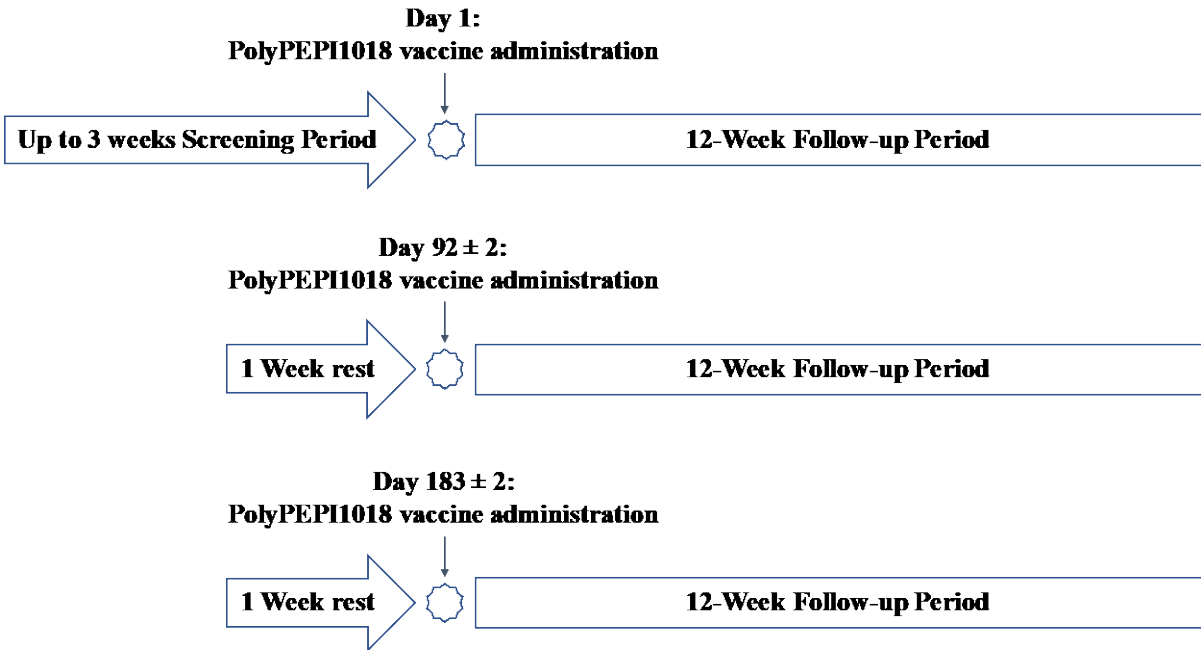
The timing of the study assessments and procedures are summarized in the Schedule of Study Assessments (SoA) in Appendix A.

Figure 3. Study Design Schema

Five subjects in Italy will follow the original Study Design



Ten Subjects in the USA will follow the amended Study Design; those who have already signed an Informed Consent Form for the original Study Design will be asked to sign a new Informed Consent Form at the end of the first 12-week follow-up period.



3.2 Outcome Measures

3.2.1 Primary Outcome Measures

- The incidence and severity of all adverse events (AEs), related AEs, all SAEs, related SAEs, and temporally-associated AEs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (v4.0)
- Change from baseline in clinical laboratory safety parameters and vital signs
- Number and proportion of subjects with any clinically significant change in vital signs (i.e., blood pressure, pulse rate, respiratory rate, body temperature) during the vaccine administration or within 60 minutes following administration

3.2.2 Secondary Outcome Measures

- PEPIs as identified by the PEPI Test
- Effector T cell response against 12 selected epitopes of PolyPEPI1018 as measured by interferon (IFN)-gamma Enzyme-Linked ImmunoSpot (ELISPOT) assay for the following:
    - Number and proportion of subjects with 0, ≥1, ≥2, ≥3, ≥4, ≥5 effector T cell responses, respectively, detected at the Baseline Visits (Week -3 to -1 and Week 0) and at 3, 6-, 9-, and 12-weeks after administration of the vaccine
    - For each subject, the number of effector T cell responses
    - For each subject, the time course of effector T cell response at Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine

- Memory T cell response against 12 selected epitopes of PolyPEPI1018 as measured by the Precursors with High Proliferation Capacity (PHPC) assay for the following:
    - Number and proportion of subjects with 0, ≥1, ≥2, ≥3, ≥4, ≥5 memory T cell response, respectively, detected at the Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine
    - For each subject, the number of positive memory T cell responses
    - For each subject, the time course of memory T cell response at Baseline Visits (Week -3 to -1 and Week 0) and at 3-, 6-, 9-, and 12-weeks after administration of the vaccine
- Objective Response Rate (ORR) measured by CT scan at Screening Visit (Week -3 to -1), and at 6-, and 12-weeks after administration of each dose of the vaccine

3.2.3 Exploratory Outcome Measures

- Correlations between PEPIs identified by the PEPI Test and effector and memory T cell responses measured by ELISPOT and PHPC immunogenicity assays
- Change in relative counts of TILs in accessible tumor biopsies at Baseline (Week -3 to -1) and at Week 12 as measured by immunohistochemistry
- Correlation between PEPIs identified by the PEPI Test and infiltrating lymphocyte in tumor biopsies measured by immunohistochemistry
- Correlations between T cell responses measured by ELISPOT and PHPC and infiltrating lymphocyte in tumor biopsies measured by immunohistochemistry
- Correlations between PEPIs identified by the PEPI Test and effector and ORR
- Correlations between T cell responses measured by ELISPOT and PHPC and ORR

3.3 Estimated Study Duration

Four out of ten subjects have already been accrued under the original single-dose Study Design, the first one being accrued in May 2017. These subjects will be asked to sign a new informed consent for multiple dosing and it is anticipated that they will be willing to agree. It is also anticipated that subject accrual rate for the remaining six subjects will be one subject every 20 days. Based on this rate it will take approximately 4 months to accrue a total of 10 subjects. Since subjects are followed for 38 weeks after the PolyPEPI1018 initial vaccination, the total duration of the study is approximately 14 months from the date of amendment, that is approximately 17 months from the initiation of the OBERTO study.

3.4 Randomization and Blinding

This is a non-randomized, open-label study.

3.5 Study Stopping Rules

The sponsor has the right to terminate the study at any time. The study will be stopped if any of the following occur:

- New information leading to an unfavorable risk-benefit judgement of PolyPEPI1018, including the following (applicable after every vaccination and every five patients):
    - 3 or more DLTs within 21 days of peptide vaccine administration
    - 1 or more deaths (other than death related to progressive disease) that occurs within 30 days of peptide vaccine administration
    - Other unfavorable safety findings
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons
- Poor enrollment of subjects making completion of the study within an acceptable time frame unlikely
- Discontinuation of the development of PolyPEPI1018
- Specific request of a health authority

In accordance with applicable regulations, health authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed by the sponsor if the study is discontinued.

If a study is discontinued, the investigator will inform the subject's primary health care provider, as applicable, to ensure the subject receives the appropriate follow-up and care.

4 SUBJECT SELECTION

A total of 10 subjects with mCRC who have achieved partial response (PR) or stable disease during first-line treatment with chemotherapy plus a biologic drug will be enrolled.

4.1 Inclusion Criteria

Subjects who meet ALL of the following criteria are eligible for this study:

1. Male or female subjects, 18-75 years of age at time of Screening who provide written informed consent prior to initiation of any study procedure
2. Histologically confirmed metastatic adenocarcinoma originating from the colon or the rectum
3. Presence of at least 1 measurable reference lesion according to the RECIST version 1.1 criteria
4. Experienced PR or stable disease during first-line treatment with a systemic chemotherapy regimen and 1 biological therapy regimen
5. Maintenance therapy with a fluoropyrimidine (5-fluorouracil or capecitabine) plus the same biologic agent (bevacizumab, cetuximab or panitumumab) used during induction, scheduled to initiate prior to the first day of treatment with the study drug
6. No more than 1 line of chemotherapy regimen for mCRC (adjuvant therapy for non-metastasized disease is allowed if terminated more than 6 months before Screening and without recurrence within 6 months after the end of adjuvant treatment)
7. Last CT scan at 3 weeks or less before the first day of treatment
8. ECOG performance status of 0 or 1
9. Women of childbearing potential must agree to appropriately use an effective form of contraception (failure rate of <1% per year) for 3 months from the day of the treatment. An effective form of contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm, cervical cap or condom
10. Men must agree to use an effective form of contraception (as defined above), and not donate sperm for 3 months from the day of the treatment
11. White blood cell count $\geq 3.0 \times 10^9$/L with neutrophils $\geq 1.5 \times 10^9$/L
12. Platelets $\geq 100 \times 10^9$/L, hemoglobin ≥5.6 mmol/L (corresponding to 9 g/dL)
13. Serum bilirubin ≤1.5 × upper limit of normal (ULN) set by the site

14. Alanine amino transferase (ALAT) and aspartate amino transferase (ASAT) ≤2.5 × ULN in the absence of liver metastases. ALAT and ASAT ≤5 × ULN set by the site in the presence of liver metastases
15. Serum creatinine ≤1.5 × ULN set by the site and creatinine clearance >30 mL/min using Cockroft formula
16. Relevant toxicities of prior therapies must have resolved, except for oxaliplatin-related neuropathy or alopecia
17. Anticipated life expectancy ≥6 months
18. Subject is willing and able to comply with the requirements of the protocol

4.2 Exclusion Criteria

Subjects who meet ANY of the following criteria are not eligible for this study:

1. Received chronic systemic immune therapy or immunosuppressant medication other than steroids within the last 6 weeks prior to start of study treatment
2. Received continuous systemic steroid treatment within the last 2 weeks prior to start of study treatment
3. Colorectal cancer with documented MSI-H
4. Colorectal cancer with documented BRAF mutations
5. Pre-existing systemic autoimmune or antibody-mediated diseases or immune deficiency diseases
6. Central nervous system (CNS) metastases
7. Active or uncontrolled severe infections or undiagnosed febrile condition >38ºC
8. Acute or subacute intestinal obstruction or history of chronic intestinal inflammatory diseases
9. Symptomatic peritoneal carcinomatosis
10. Peritonitis
11. Serious, non-healing wounds, ulcers or bone fractures
12. Nephrotic syndrome
13. Arterial thromboembolisms or severe hemorrhages within 6 months before study enrolment (except bleeding tumor before tumor resection surgery)
14. Hemorrhagic diathesis or thrombotic tendency
15. Major surgery or radiotherapy within 12 weeks prior to the study treatment or anticipation of needing such procedure during the study period

16. Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days
17. Participants with active malignancy (other than CRC) or a prior malignancy within the past 12 months
18. Participant with myocardial infarction within 6 months prior to enrollment or New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to the first dose of study treatment, any electrocardiogram (ECG) abnormality at screening must be documented by the investigator as not medically relevant
19. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of a live attenuated vaccine will be required during the study
20. Participant has participated in another clinical study involving an investigational product (IP) or investigational device within 30 days prior to enrollment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study
21. Known hypersensitivity to any component of the investigational drug
22. If female, participant is pregnant (exclusion confirmed with beta-human chorionic gonadotropin [hCG] test) or lactating at the time of enrollment, or has plans to become pregnant or start breastfeeding during the study
23. Pre-existing alcohol or drug abuse
24. Medical or mental impairments which make it impossible to obtain the patient's consent or to conduct the study
25. A significant concomitant medical condition which the clinical investigator believes precludes the patient from enrolling in the study
26. Absent or limited legal competence

4.3 Subject Withdrawal and Discontinuation

Any subject may voluntarily withdraw consent (i.e., reduce the degree of participation in the study) for aspects of continued participation and data collection. The reason for withdrawal will be recorded on the End of Study Case Report Form (CRF). Assessments to be performed at the Last Visit are described in Section 7.4.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e., discontinuation by subject without notice or action). Additionally, the investigator and sponsor have the discretion to

discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

During the initial study period, that is during the 12 weeks following the first vaccination, if a patient experiences disease progression and needs to start a second-line therapy, the patient will be withdrawn from the study. This is required to obtain a complete (12 weeks) measurement of the immunological response curve after the initial vaccination, that is one of the original study objectives. In contrast, if a patient experiences disease progression and needs to start a second-line therapy after the second vaccination, the patient will remain in the study, receive the third vaccination as scheduled and complete follow-up. This will allow to gain a better sense of initial efficacy of the PolyPEPI1018 vaccine, that is another study objective.

If a subject must be withdrawn from the study, the responsible designee medical monitor will be informed immediately, and this person will then notify the sponsor's medically responsible party. All subjects who prematurely discontinue from the study, regardless of cause, should be seen as soon as possible and undergo the assessments specified for the Last Visit (see Section 7.4).

If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned or health has stabilized. The investigator will inform the subject's primary health care provider (as applicable) as agreed by the subject, to ensure the subject receives the appropriate follow-up and care.

If the subject is prematurely discontinuing due to withdrawal of consent, the investigator should clarify the level of consent withdrawal with the subject (i.e., consent withdrawal with regard to permission to utilize samples already collected but not analyzed and willingness to return for safety follow-up assessments). The level of consent withdrawal should be documented this in the electronic case report form (eCRF)

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator

should show "due diligence" by documenting in the source documents all steps taken to contact the subject (e.g., dates of telephone calls and registered letters).

Subjects who discontinue or are withdrawn from the study, including withdrawal after receipt of the study's IP on or after Day 1 of Week 0, will be replaced, except for subjects who experience a DLT: a subject who experiences a DLT will be withdrawn from the study and will not be replaced.

4.3.1 Permanent Treatment Discontinuation

Subjects will be permanently withdrawn from treatment for the following reasons:

- Vaccine-related toxicity (Section 5.5)
- Requirement of prohibited concomitant medications (Section 5.4.2)
- Request by subject to terminate study
- Completion of the study treatment as defined by the protocol
- Clinical reasons believed life threatening by the physician, even if not addressed in Section 5.5

4.3.2 Premature Treatment Discontinuation

Subjects will be prematurely discontinued from treatment for the following reasons:

- Failure by the subject to attend two consecutive clinic visits
- Request by the subject to withdraw
- Pregnancy
- Development of an exclusionary condition as outlined in Section 4.2
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- Subject reaches a defined study endpoint, as outlined in Section 3.2, if applicable
- At the discretion of the health authority, IRB/IEC, investigator, or pharmaceutical supporter

5 STUDY TREATMENTS

5.1 PolyPEPI1018 CRC Vaccine

5.1.1 Description

5.1.1.1 Vaccine Substance

The vaccine is composed of 6 synthetic peptides and is manufactured according to Good Manufacturing Practices (GMP) using solid phase peptide synthesis. The vaccine substance should be stored in vials as a peptide solution (0.2 mg/mL in DMSO/water) at -20ºC.

5.1.1.2 Adjuvant

The adjuvant Montanide™ (ISA 51 VG) is a mixture of highly purified mineral oil and mannide monooleate (derived from vegetable grade olive oil). It is manufactured according to GMP and should be stored in vials as an emulsion at room temperature.

5.1.2 PolyPEPI1018 Product Preparation and Administration

PolyPEPI1018 final vaccine product will be prepared at the clinical site prior to injection by the physician or the nurse according to standard operating procedure and should be administered as soon as possible following preparation.

The peptide solutions (see Section 5.1.1.1) should be thawed and incubated at room temperature with the adjuvant Montanide™. A 4-mL volume of the final PolyPEPI1018 product will be prepared by mixing (emulsifying) each of the peptide solutions with an equal volume of the adjuvant Montanide™. Each dose of the final PolyPEPI1018 product will contain 0.8 mg peptides per 1 mL (4 peptides) solution + 0.4 mg peptides per 1 mL (2 peptides) solution plus 2 mL adjuvant.

Prior to the PolyPEPI1018 administration, the subject's body temperature should be checked and the vaccine should only be administered if the subject's body temperature is <38ºC.

Each subject will receive a total of four 1 mL SC injections of the final PolyPEPI1018 product (i.e., one 1 mL SC injection per predetermined anatomic site, (preferably draining to axillary or inguinal lymph nodes). A pause of a few minutes should be observed after the first

injection to check for side effects. The remaining injections can be subsequently administered without pause.

Additional details are provided in the Study Procedures Manual.

5.1.3 Packaging and Labeling

PolyPEPI1018 peptide solutions will be supplied in pre-labeled boxes by the sponsor and the labels will be compliant with country specific regulatory requirements. Each box will contain vials of PolyPEPI1018-Mix1 and vials of PolyPEPI1018-Mix2 that needs to be stored in the freezer (-20ºC). Each box will contain a label firmly attached to the box, with the company name, lot number, storage temperature, expiry date and a statement that the box contains vials of PolyPEPI1018-Mix1 and PolyPEPI1018-Mix2, respectively. Vials themselves will have label containing the vaccine name and lot number, content of the vial, strength of the solution, route of administration and storage temperature. One vial of each box will be used per subject for the preparation of the vaccine product at the clinical site.

Adjuvant Montanide™ will be shipped by Seppic in pre-labeled boxes that need to be stored at room temperature (15ºC to 30ºC). Each box will contain 3 mL vials labeled as Montanide™ ISA 51 VG sterile, lot number, composition, manufacturer and expiration date. One vial will be used per peptide mixture, 2 vials per subject.

5.1.4 Supply, Distribution, and Pharmacy

The following study supplies are needed and will be provided as described below:

- PolyPEPI1018 vials will be distributed by the sponsor as described in Section 5.1.3.
- Montanide™ adjuvant will be distributed by the supplier, Seppic SA, as described in Section 5.1.3.
- Single use plastic equipment for PolyPEPI1018 vaccine emulsification procedure will be supplied by the Sponsor. Syringes, I-connector and vial adapters will be packaged together without harming the individual sterile packing of the devices. Each set will contain enough supplies for one emulsification procedure.

  Each package contains:
  - 2 pieces of Disposable latex, silicone and rubber free syringe (3 ml B.Braun, Injekt® Solo, VWR cat nr.: 720-2522).

- 1 piece of I-connector (Double Female Luer Lock Adapter, Promepla, Ref: ODG0015ST).
- 2 pieces of Vial adaptors (West Pharma, 13 mm, Luer Lock, sterile).

5.1.5 Storage

5.1.5.1 PolyPEPI1018

Intact vials containing PolyPEPI1018 should be stored between -25ºC and -15ºC. Thawed vials may be stored for up to 3 hours at room temperature. Re-freezing is not allowed. Records must be available showing periodic temperature checks of storage freezer material.

Vaccine emulsions consisting of peptide admixed with Montanide™ are stable for 4 hours at 4ºC, but should be administered as soon as possible following preparation.

5.1.5.2 Adjuvant

Montanide™ should be stored between 15ºC and 30ºC.

5.2 Reference Therapy

Not applicable

5.3 Investigational Product Accountability

The investigator will ensure that the IP (i.e., PolyPEPI1018 and Montanide™) is stored as specified in Section 5.1.5 and that the storage area is secured, with access limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. The IP must be dispensed only at the study site or other suitable location. Records will be maintained that includes the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP(s) will be returned to the sponsor or sponsor's representative after study completion/termination, or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures. If IP(s) is to be destroyed, the investigator will provide documentation in accordance with sponsor's specifications.

5.4 Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications from the initiation of the first-line CRC therapy until 85 days after the subject's vaccination must be recorded on the eCRF.

5.4.1 Required Medications

Subjects must be on maintenance therapy with a fluoropyrimidine (5-fluorouracil or capecitabine) plus the same biologic agent (bevacizumab, cetuximab or panitumumab) used during induction, prior to Day 1 (Week 0, Visit 2). Modifications may be allowed for toxicity/tolerability reasons, but must be approved by the medical monitor to determine whether the subject can remain on study treatment/on study.

5.4.2 Prohibited Medications

The concomitant use of the following immunomodulator therapies, which have potential putative effects on immunologic and/or virologic indices, are prohibited while on study:

- Systemic (intravenous and oral) corticosteroids
- Thalidomide
- Cyclosporine
- Interferons
- Interleukins
- IgG-containing products
- Cimetidine (Tagamet)
- Acetylcysteine (NAC)
- Sargramostim (GM-CSF)
- Dinitrochlorobenzene (DNCB)
- Thymosin alpha 1 (thymosin alpha)
- Thymopentin
- Inosiplex (Isoprinosine)
- Polyribonucleoside (Ampligen)

- Ditiocarb sodium (Imuthiol)
- Hydroxyurea
- Checkpoint Inhibitors
- Experimental vaccines
- Investigational agents

5.4.3 Precautionary Medications

The following medications may be used during the study with caution:

- Treatment with topical corticosteroids is allowed except at the proposed vaccination sites within 2 weeks prior to vaccination
- Use of local skin treatments is allowed, except in the targeted vaccination sites, within 2 weeks prior to vaccination. During the vaccination period, subjects should avoid manipulation of vaccinated areas to enable monitoring of possible vaccine-related toxicity. Sites may be rinsed with water, but soap and other possible irritants should be avoided. In the case of discomfort at the vaccination site, cold packs may be administered as needed. All other local treatments should only be administered after consultation with the investigator.

5.5 Dose Modification Guidelines and Toxicity Management

A safety review team, internal to the sponsor, will regularly monitor all aspects of patient safety throughout this study. This team will be comprised of the medical monitor, a statistician, and ad hoc authorized representatives as appropriate. The safety review team will meet regularly to review all SAEs and will examine non-serious AEs, clinical laboratory data and other relevant safety data.

5.5.1 Local Reactions

Local reactions, resulting from the vaccine will be graded using the local reaction assessment scale (Table 2).

Table 2. Local Reaction Assessment Scale

Grade	Description
0 = None	Not Applicable.
1 = Mild	Macular or papular eruption, erythema, or induration that is asymptomatic or mildly symptomatic.
2 = Moderate	Macular or papular eruption, erythema or induration with pruritus, or other associated moderate symptoms.
3 = Severe	Ulceration, superinfection, blistering, or phlebitis.
4 = Potentially Life-Threatening	Necrosis of the skin.

If the subject develops a potentially life-threatening (Grade 4) local reaction thought to be probably or definitely related to vaccination, the safety review team must be notified within 24 hours.

The safety review team will determine whether local reactions are due to the vaccine.

5.5.2 Systemic Reactions

Systemic reactions will be graded according to the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Cox 2010) (Appendix B).

The safety review team should be contacted within 48 hours for any non-local Grade 3 or 4 reactions (i.e., elevated temperature following vaccinations) thought probably or definitely related to vaccination.

The safety review team will determine whether systemic reactions are due to the vaccine.

5.5.3 Anticancer Drugs

Unanticipated and anticipated toxicities from the anticancer maintenance therapy regimen will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Any Grade 3 or 4 toxicities that result in a temporary or permanent change in an anticancer therapy must be reported to the safety review team within 4 days of knowledge of the change.

Anticipated toxicities resulting from components of the anticancer maintenance therapy regimen will be managed by the subject's clinician according to best clinical practice including dose reductions when indicated.

Subjects who change and/or permanently discontinue their anticancer maintenance therapy will be handled on a case-by-case basis through discussions with the safety review team to decide whether they can remain on study treatment/on study.

5.5.4 Dose Limiting Toxicity (DLT)

DLT is defined as any of the following occurring any time from Day 1 (Visit 2) until 21 days after administration of the vaccine (according to NCI CTCAE version 4.0, (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm):

Hematologic

- Grade 4 hematologic toxicity which lasts at least 5 days
- Grade 3 or higher thrombocytopenia which lasts at least 5 days

Non-hematologic:

- Grade 4 or greater non-hematological local (at the site of vaccine injection) adverse events
- Grade 3 or greater non-hematological systemic adverse events with the exception of alopecia, anorexia, nausea, vomiting and fatigue, constipation and dehydration

6 DESCRIPTION OF STUDY ASSESSMENTS AND PROCEDURES

The timing of the study assessments and procedures are summarized in the SoA in Appendix A.

The investigator and sponsor will conduct the study in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct, and the investigator must ensure that study procedures are performed as described in the protocol. During the study, procedures and observations will be monitored to confirm that study requirements are being followed as outlined in the SoA.

6.1 Informed Consent Form

Any patient who provides informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered a subject in the study. Subjects presently on study who have signed an informed consent form for a single vaccination will be asked to sign a new informed consent form for multiple (N=3) vaccinations.

6.2 Subject Identification Code

The following series of numbers will comprise the SIC: protocol identifier (e.g., 090701) to be provided by the sponsor, 2- or 3-digit study site number (e.g., 02) to be provided by the sponsor, and 3- or 4-digit subject number (e.g., 0003) reflecting the order of providing informed consent. For example, the third subject who signed an informed consent form at the site 02 will be identified as Subject 090701-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC. Additionally, a uniquely coded SIC(s) is permitted if it does not contain a combination of information that allows identification of a subject (e.g., collection of a subject's initials and birth date would not be permitted), in compliance with laws governing data privacy.

6.3 Screening Log

The study site is responsible for maintaining a Screening log that includes all subjects who provided informed consent. The log also will serve to document the reason for screening

failure. All screening data will be collected and reported in CRFs, regardless of screening outcome. If a subject is re-screened, the End of Study CRF should be completed, and a new informed consent form (ICF), new SIC and new CRF are required for that subject.

6.4 Vaccine Site Evaluation

A vaccine site evaluation for local and/or systemic adverse reactions will be performed in the clinic 1 hour after vaccination. If there are no adverse reactions noted within 1 hour after vaccination, subjects may be released from the clinic.

Results of the site evaluation and toxicity grade, if appropriate, must be recorded in the source documents and documented on the CRF.

For subsequent visits, vaccine site evaluation must be repeated.

The following vaccination steps must be recorded in the source documents and documented on the CRF:

- Vaccination sites
- Disinfection of vaccination sites
- Time of application

6.5 Evaluation of Response to First-line Therapy

During the Screening Period, results from a CT scan which was performed at the completion of the first-line treatment regimen must be obtained (i.e., eligibility CT scan). The results will be evaluated by the investigator and must confirm that the subject has responded to first-line chemotherapy with documentation of cancer regression or lack of progression, according to RECIST version 1.1 criteria (https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf)

6.6 Immunogenicity and Efficacy Assessments

The following immunogenicity and efficacy parameters will be assessed:

- PEPI Test
- Effector T cell response
- Memory T cell response

- TILs assessment
- CT assessment

6.6.1 PEPI Test

To identify PEPIs the sponsor developed a novel PEPI Test. The PEPI Test selects from HLA restricted epitopes certain PEPIs that are capable of activating T cells in an individual. PEPIs are genetic biomarkers specific to the HLA genotype of an individual patient. The PEPI Test will be used to identify PEPIs among the 12 selected epitopes of PolyPEPI1018 in each study subject.

To perform the PEPI Test a buccal swab sample will be collected on Day 1 (Visit 2) and sent to LabCorp for HLA genotyping. LabCorp will send the HLA genotype data to Treos Bio ZRT (sponsor) to perform the PEPI Test. The sponsor will perform the PEPI Test before any immunology or efficacy assessment becomes available, essentially in a blinded fashion. The PEPI Test results will be unblinded and the data compared with immunology and efficacy results as described in Section 9.5.2.

6.6.2 Effector T Cell Response

Effector T cells are generated through activation of naïve or memory T cells following recognition of epitopes presented by the HLA molecules. ELISPOT assay is a routine test to be utilized for the detection of effector T cells that respond to PolyPEPI1018 treatment from a population of peripheral blood mononuclear cells (PBMCs).

6.6.3 Memory T Cell Response

Memory T cells are a subset of antigen specific T cells that previously encountered and responded to their cognate epitope. Such T cells are primed by HLA-restricted peptides and originate either from cancer cells or from the vaccine. During a second activation, memory T cells can proliferate faster than during priming. This behavior is captured by the PHPC assay, abbreviated from “T cell precursors with high proliferation capacity” that allows the expansion of memory cells during prolonged culture and then detects the progeny of the antigen-specific memory T cell clone by IFN-γ ELISPOT. It has been previously

demonstrated that the PHPC assay identifies expandable memory T cells that can reveal previous exposure to specific peptide antigens (Calarota 2008).

6.6.4 Tumor Infiltrating Lymphocyte (TILs)

The presence of TILs is associated with favorable long-term outcome in several cancers, including breast cancer and CRC (DeNardo 2007; Schmidt 2008; Klintrup 2005).

During the procedure tumor specimens are fixed in 10% formalin, embedded in paraffin, and 4-µm-thick sections are prepared for hematoxylin and eosin staining or other appropriate staining and immunohistochemistry (IHC). All stainings and data reading are performed and reviewed by the same pathologist. The unused tumor sections will be retained according to the site procedure.

TILs are assessed according to published criteria (Klintrup 2005) using a 4-degree scale at the deepest area of the invasive margin. A score of 0 is given when there is no increase in inflammatory cells, 1 denotes a mild and patchy increase in inflammatory cells, 2 denotes a moderate and band like inflammatory infiltrate with some destruction of cancer cell islands, and 3 denotes a marked and florid cuplike inflammatory infiltrate with frequent destruction of cancer cell islands. These scores can be subsequently classified as low grade (scores 0 and 1) and high grade (scores 2 and 3).

6.6.5 CT scan and RECIST/ irRECIST evaluation

CT scan will be performed at the site and original data will be retained either in a CD-ROM format or in a data room.

RECIST criteria will be evaluated at baseline, week 6 (Visit 4), week 12 (Visit 6), week 25 (Visit 11), week 38 (Visit 16) based on the CT scan results. If progressive disease (PD) is suspected at week 6, irRECIST evaluation (https://www.parexel.com/files/7914/2186/7838/irrecist-path-PDF.pdf) will be implemented; if the subject remains in the study, the CT scan on Wk 12 will be evaluated according to irRECIST criteria.

6.7 Safety Assessments

6.7.1 Adverse Events

Details on definitions and reporting of AEs are provided in Section 8.

All AEs will be recorded from the time of signing of the ICF until completion of the Last Visit. Patients should be monitored for AEs consistent with the current Investigator's Brochure for PolyPEPI1018.

6.7.2 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, to protect subjects participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the by the investigator or the safety review team, and may include any of the following:

1. Immediate change in study design or study procedures
2. Temporary or permanent halt of a given clinical trial or trials
3. Any other immediate action taken to protect clinical trial participants from immediate hazard to their health and safety

The investigator or the safety review team may take appropriate urgent safety measures to protect subjects against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorization from the sponsor. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the medical monitor immediately by phone and confirm notification to the safety review team in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible ethics committee(s) and relevant competent authority(s) are notified of the urgent safety measures taken in such cases according to local regulations.

6.7.3 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP are not considered AEs (according to the definition of AE, see Section 8). However, each serious untoward medical occurrence experienced before the IP exposure (i.e., from the time of signed

informed consent up to but not including the IP exposure) will be described on the AE CRF and on the SAE Report Form. These events will not be considered as SAEs and will not be included in the analysis of SAEs.

For the purposes of this study, each non-serious untoward medical occurrence experienced by a subject undergoing study-related procedure(s) before the IP exposure will be recorded on the AE CRF; these events will not be considered as AEs and will not be included in the analysis of AEs.

6.7.4 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, and performance of the product but did not result in an AE. NMCs include but are not limited to the following:

1. A failure of a product to exhibit its expected pharmacological activity and/or design function, e.g. reconstitution difficulty
2. Missing components
3. Damage to the product or unit carton
4. A mislabeled product (e.g., potential counterfeiting/tampering)
5. A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

6.7.5 Medical, Medication, and Non-Drug Therapy History

At Screening, the subject's medical history will be described for the following body systems including severity (defined in Section 8.2.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from 3 months prior to enrollment until completion/termination will be recorded on the concomitant medications and non-drug therapies CRFs.

6.7.6 Physical Examinations

Complete and targeted physical examinations will be performed as summarized in Appendix A.

Complete physical examinations will be performed on the following body systems: general appearance, signs and symptoms (including, but not limited to the head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological). Moreover, diagnoses, Karnofsky score, height, weight and vital signs will be registered. Finally, skin observation will be performed.

At Screening, if an abnormal condition is detected, the condition will be described on the medical history CRF. At study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF. If the abnormal value was not deemed an AE because it was due to an error, due to a preexisting disease (described in Section 8.1.6), not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the source record.

At Visits 3 and 5, a targeted physical examination including vital signs should be driven by any new or previously identified signs and symptoms that the subject has experienced since the last visit.

6.7.7 Vital Signs

Vital sign values (including seated blood pressure, pulse, respirations, and oral temperature) are to be measured at every visit as part of the complete and targeted physical examinations, and recorded on the CRF. At Day 1, measurement of vital signs must be performed in two occasions: before vaccination and 1 hour after last vaccination. For each abnormal vital sign value, the investigator will determine whether to report an AE (see definition in Section 8.1.1 and record the medical diagnosis [preferably], symptom, or sign on the AE CRF) to the

safety review team. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

6.7.8 Clinical Laboratory Parameters

6.7.8.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, ALAT, ASAT, gamma-glutamyl transpeptidase, total bilirubin, uric acid, blood urea nitrogen, creatinine, lactate dehydrogenase, creatine phosphokinase, alkaline phosphatase and glucose.

Urinalysis will include description of color and clarity, specific gravity, pH, content of protein, glucose, nitrites and ketones. A microscopic analysis will be performed to check for red or white blood cells, casts, crystals, bacteria, yeast cells, parasites, and squamous cells.

Urine and blood samples will be obtained for assessment of hematology and clinical chemistry at Screening, at Visit 2 (Day 1, Week 0), Visit 4 (Week 6), Visit 6 (Week 12), Visit 9 (Week 19), Visit 11 (Week 25), Visit 14 (Week 32) and Visit 16 (Week 38). Hematology and clinical chemistry assessments will be performed at the local laboratory at the investigator site.

6.7.8.2 Tumor Biomarkers

Blood samples will be collected to evaluate tumor biomarkers, including carcinoembryonic antigen (CEA) and cancer antigen (CA 19-9).

6.7.8.3 Assessment of Laboratory Values

6.7.8.3.1 Assessment of Abnormal Laboratory Values

The investigator's assessment of each laboratory value will be recorded on the CRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the value constitutes a new AE (see definition in Section 8.1.1, and record the sign, symptom, or medical diagnosis on the AE CRF), is a symptom or related to a previously recorded AE, is due to a pre-existing disease (described in Section 8.2.2), or is due to another issue that will be specified. If the abnormal value was not clinically significant, the investigator will indicate the reason, i.e., because it is due to a preexisting disease, due to a lab error, or due to another issue that will be specified. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. The investigator will communicate the AE to the safety review team for final evaluation.

6.7.9 Patient Diary

A subject diary will be distributed to subjects on Day 1 (Visit 2), Day 92 ±2 (Visit 7) and Day 183 ±2 (Visit 12) to collect local signs related to the injection sites, physical fatigue, and body temperature during the first two weeks after the injection. Temperature should be consistently measured at the same location (e.g. underarm, ear, mouth etc.).

6.8 Procedures for Monitoring Subject Compliance

All study procedures are to be performed under the direct supervision of the investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

7 ASSESSMENTS AND PROCEDURES BY STUDY VISIT

The timing of the study assessments and procedures are summarized in the SoA (Appendix A). Note: At the end of the follow up period (that is 12 weeks after each vaccination), ideally one week rest period should be observed before the next vaccination, as described in the SoA. However, up to 1 month rest period is allowed.

7.1 Screening Period (Visit 1 - Days -21 to Day -1 – Weeks -3 to -1)

The following procedures will be performed at the Screening Visit:

- Informed consent
- Inclusion/exclusion criteria
- ECOG performance status
- Medical history
- Medication history
- Complete physical exam
- Evaluation of response to first-line therapy
- Cancer biopsy for TIL analysis
- CT and RECIST assessment
- Hematology and blood chemistries
- Tumor biomarkers
- Urinalysis
- Urine pregnancy test
- Blood collection for immunogenicity assays

7.2 PolyPEPI1018 Administration (Visit 2 – Day 1 - Week 0), (Visit 7 – Day 92 ±2 - Week 13) and (Visit 12 – Day 183 ±2 - Week 26),

The following procedures will be performed at Visits 2, 7 and 12:

- Concomitant medications
- Complete physical exam
- Vaccine site evaluation
- Buccal swab
- Vaccine administration and 1-hour post-vaccination observation

- Distribute diary
- Hematology and blood chemistries (not on Visits 7 and 12)
- Tumor biomarkers (not on Visits 7 and 12)
- Urinalysis (not on Visits 7 and 12)
- Urine Pregnancy Test (not on Visits 7 and 12)
- Blood Collection for Immunogenicity Assays (not on Visits 7 and 12)

7.3 Follow-Up Period

7.3.1 Visit 3 (Day 22 - Week 3), Visit 5 (Day 64 - Week 9), Visit 8 (Day 113 ±2 - Week 16), Visit 10 (Day 155 ±2 - Week 22), Visit 13 (Day 204 ±2 - Week 29) and Visit 15 (Day 246 ±2 - Week 35)

The following procedures will be performed at Visits 3, 5, 8, 10, 13 and 15:

- Concomitant medications
- Targeted physical exam
- Vaccine site evaluation
- Collect diary
- Blood collection for immunogenicity assays

7.3.2 Visit 4 (Day 43 - Week 6), Visit 6 (Day 85 - Week 12), Visit 9 (Day 134 ±2 - Week 19), Visit 11 (Day 176 ±2 - Week 25), Visit 14 (Day 225 ±2 - Week 32) and Visit 16 (Day 267 ±2 - Week 38)

The following procedures will be performed at Visits 4, 6, 9, 11, 14 and 16:

- Concomitant medications
- Complete physical exam
- Vaccine site evaluation
- Collect diary
- CT and RECIST assessment (irRECIST assessment for subjects suspected of progression diseases at Visit 4)
- Hematology and blood chemistries
- Tumor biomarkers
- Urinalysis
- Urine pregnancy test

- Blood collection for immunogenicity assays
- Cancer biopsy for TIL analysis (only at Visit 6)

7.4 Last Visit

Every effort will be made to have discontinued, withdrawn, and terminated subjects complete the assessments described for Visit 16 (see Section 7.3.2). If the Last Visit is performed as an unscheduled visit, the assessment results will be recorded with the Last Visit. If a subject terminates participation in the study and does not return for the Visit 16 assessments, their last recorded assessments shall remain recorded with their last visit. The reason for discontinuation will be recorded, and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Timely collection and assessment of SAE reports are critical for protecting the safety of patients. SAE reporting is a regulatory responsibility of the Sponsor under the Code of Federal Regulations (Title 21, Sub-Part B, section 312.32).

8.1 Definitions

8.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered an IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., rash, pain, discomfort, fever, dizziness, etc.), disease (e.g., peritonitis, bacteremia, etc.), or outcome of death temporally associated with the use of an IP, whether considered causally related to the IP.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

8.1.2 Serious Adverse Event

An SAE is defined as an untoward medical occurrence that at any dose meets 1 or more of the following criteria:

1. Outcome is fatal/results in death (including fetal death).
2. Is life-threatening – defined as an event in which the subject was, in the judgment of the safety review team, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay.
4. Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
5. Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above.

8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected.

The event(s) must meet all the following:

- Suspected adverse reaction
- Serious
- Unexpected
- Assessed as related to study treatment

Once determined to meet the criteria for a SUSAR, an SAE should be submitted to regulatory agencies expeditiously.

8.1.4 Non-Serious Adverse Event

A non-serious AE is an AE that does not meet the criteria of an SAE.

8.1.5 Unexpected Adverse Events

An unexpected adverse event is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the Reference Safety Information (RSI). “Unexpected” also refers to the AEs that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the product under investigation. The expectedness of AEs will be determined by the sponsor using the Investigator’s Brochure as the RSI. This determination will include considerations such as the number of AEs previously observed, but not on the basis of what might be anticipated form the pharmacological properties of a product.

8.1.6 Preexisting Diseases

Preexisting diseases that are present before entry in to the study are described in the medical history, and those that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity, duration, or frequency of a preexisting disease, the event must be described on the AE CRF.

8.2 Assessment of Adverse Events

Each AE from the IP exposure until study completion/discontinuation date will be described on the AE CRF using the medical diagnosis (preferred), or, if no diagnosis could be established at the time of reporting the AE, a symptom or sign, in standard medical terminology to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 8.1). Each AE will be evaluated by the safety review team for:

1. Seriousness as defined in Section 8.1.2
2. Severity as defined in Section 8.2.1
3. Causal relationship to IP exposure or study procedure as defined in Section 8.2.2

For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable (e.g. for maintenance therapy drugs) action taken (i.e., dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown) will also be recorded on the AE CRF. AEs attribution must be clearly specified, whether it is attributed to the vaccine or to maintenance drugs or any other concomitant medication. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion, whichever comes first). If the severity rating for an ongoing AE changes before the event resolves, the original AE report will be revised (i.e., the event will not be reported as separate AE). During the course of any AE, the highest severity rating will be reported.

Deviations from the protocol-specified dosage (including overdosing, under dosing, abuse, and withdrawal), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regard to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

Any pregnancy that occurs after administration of IP to a female subject or to a male subject whose partner gets pregnant during the study period will be reported on a Pregnancy Report Form and followed-up at estimated date of delivery.

If an investigator becomes aware of an SAE occurring in a subject after study completion, the SAE must be reported on the provided SAE Report Form within 24 hours after awareness; no additional reporting on CRFs is necessary.

8.2.1 Severity

The safety review team will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below (according to CTCAE Version 4.0):

1. Mild (Grade 1)
    - Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2. Moderate (Grade 2)
    - Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3. Severe (Grade 3)
    - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4. Life threatening (Grade 4)
    - Life-threatening consequences; urgent intervention indicated
5. Death related to AE (Grade 5)
    - Grade 5 is not appropriate for some AEs and therefore is not an option

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

8.2.2 Causality

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the safety review team will assess the causal

relationship between the IP and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

1. Not related (both circumstances must be met)
    - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
    - Is not associated with the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
2. Unlikely related (either 1 or both circumstances are met)
    - Has little or no temporal relationship to the IP
    - A more likely alternative etiology exists
3. Possibly related (both circumstances must be met)
    - Follows a reasonable temporal relationship to the administration of IP
    - An alternative etiology is equally or less likely compared to the potential relationship to the IP
4. Probably related (both circumstances must be met)
    - Follows a strong temporal relationship to the administration of IP, which may include but is not limited to the following:
        - Reappearance of a similar reaction upon re-administration (positive rechallenge)
        - Positive results in a drug sensitivity test (skin test, etc.)
        - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid
    - Another etiology is unlikely or significantly less likely
5. Definitely related
    - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

9 STATISTICS

9.1 Analysis Populations

The Safety Analysis Set (SAS) will include all subjects who receive at least 1 dose of the IP. This population will be the primary analysis set for safety outcomes.

9.2 Replacement of Subjects

Any subject who withdraws from the study prematurely, or who discontinues study vaccination prematurely without experiencing a primary safety endpoint (Section 9.4) before the Day 85 (Week 12, Visit 6) evaluation, and whose reasons for withdrawing from the study, or discontinuing study vaccination administration, are unrelated to any real or perceived effect of the study vaccination or its administration, will be replaced with another subject. If possible, all subjects who discontinue study treatment prematurely will be followed for 12 weeks for all study evaluations. A maximum of 5 subjects will be replaced without asking the sponsor's permission. If more than 5 subjects need to be replaced, then the study team may, for this reason, ask the sponsor for approval.

9.3 Handling of Missing, Unused, and Spurious Data

9.3.1 Missing Data Resulting from Study Withdrawal

Only data collected from the visits by subjects will be included in the statistical analysis. No imputation will be carried out on missing values.

9.3.2 Intermediate Missing Data

Only data collected from the visits by subjects will be included in the statistical analysis. No imputation will be carried out on missing values.

9.4 Primary Endpoint

The primary endpoint is the occurrence of at least 1 ≥Grade 4 local AE or 1 ≥Grade 3 systemic AE and/or signs/symptoms, lab toxicities, and/or clinical events that is probably or definitely related to study treatment (as judged by the safety review team, including site clinicians on the team) any time from Day 1 (Visit 2) until 21 days after administration of the vaccine (Visit 3).

9.5 Statistical Analyses

9.5.1 Safety Analysis

Major components for the safety analysis will include:

- AEs solicited at every study visit, recorded, and coded according to the version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current on the date of study initiation
- SAEs
- Vital signs and physical examination findings
- Laboratory parameters

All safety assessments will be summarized in a descriptive manner similar to the analysis described in Section 9.5.1.1.

Data reported by the subjects in Patient Diary, including local signs related to the injection sites, physical fatigue, and body temperature, will be summarized in a descriptive manner.

9.5.1.1 Analysis of Adverse Events

All AEs will be analyzed in terms of descriptive statistics and qualitative analysis. Adverse events will be listed for each subject and summarized by system organ class (SOC) and preferred term according to the latest version of MedDRA. In addition, summaries of AEs by severity and relationship to IP will be presented. All safety and tolerability data recorded during the study will be listed and summarized over time, as appropriate. For the purpose of summaries and listings, the durations of AEs will be calculated as follows: (stop [day] – start [day]) + 1 day, which yields the number of days on which the AE was present.

Treatment emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of the IP. Adverse event summaries will include incidence of TEAEs, SAEs including deaths, AEs that led to IP discontinuation, AEs by maximum severity and relationship to IP, and temporally infusion related AEs. The version of the MedDRA that is current on the date of study initiation will be used throughout conduct and data analysis. All summaries will be presented by MedDRA SOC and preferred term for each treatment group.

Safety/tolerability and AE data will be presented in individual listings.

9.5.2 PEPI and Immunogenicity Analyses

Each of the 6 peptides in PolyPEPI1018 contain 2 epitopes (for a total of 12 epitopes) selected to elicit a T cell response in a high portion of subjects. The PEPI Test identifies which epitope represents a PEPI (that is capable of inducing a T cell response) in each subject. A PEPI is unique and is based on the subject's HLA genotype. Therefore, a selected epitope encoded in PolyPEPI1018 might be a PEPI for 1 individual and not for others, and vice versa. A subject may have more than 1 PEPI, or no PEPI. The PEPI Test (described in Section 6.6.1) will be performed in each subject who is enrolled in the study from the results of the HLA genotyping.

The ELISPOT assay (described in Section 6.6.2) and the PHPC assay (described in Section 6.6.3) measure effector and memory responses, respectively. These assays will be performed in each subject from blood samples collected during a time course from Baseline until the Last Visit. Based on the results of the PEPI Test and the immunogenicity tests (ELISPOT and PHPC) the secondary outcome measures will be analyzed as described in Section 3.2.2.

Immunogenicity analyses may be performed at any time during the trial, however, the results of the PEPI Test will be obtained before the results of the corresponding immunogenicity tests are available. Final analysis will be based on all data up to Day 85 (Week 12, Visit 6) for all study subjects (data from the start of study treatment of the last accrued subject through Day 85 [Week 12, Visit 6]).

9.5.3 Efficacy Analyses

Efficacy will be evaluated as Objective Response Rate (ORR) measured by CT scan at Screening Visit (Week -3 to -1), and at 6-, and 12 weeks after administration of each dose of the vaccine. RECIST and irRECIST criteria will be used.

Primary and secondary analyses will be summarized in a descriptive manner.

9.5.4 Exploratory Analyses

- Pearson correlation coefficients will be calculated to measure correlations. The significance of the correlations will be tested using standard method of estimating significance of correlations ($r\sqrt{\frac{n-2}{1-r^2}}$ follows the *t* distribution with degree of freedom *n*-2, where *r* is the Pearson correlation and *n* is the number of measurements)

- Correlated data points will be plotted and trend lines will be obtained using perpendicular (orthogonal) regression, since both axes contain measurements and/or predicted values (PEPIs predicted by the PEPI Test)

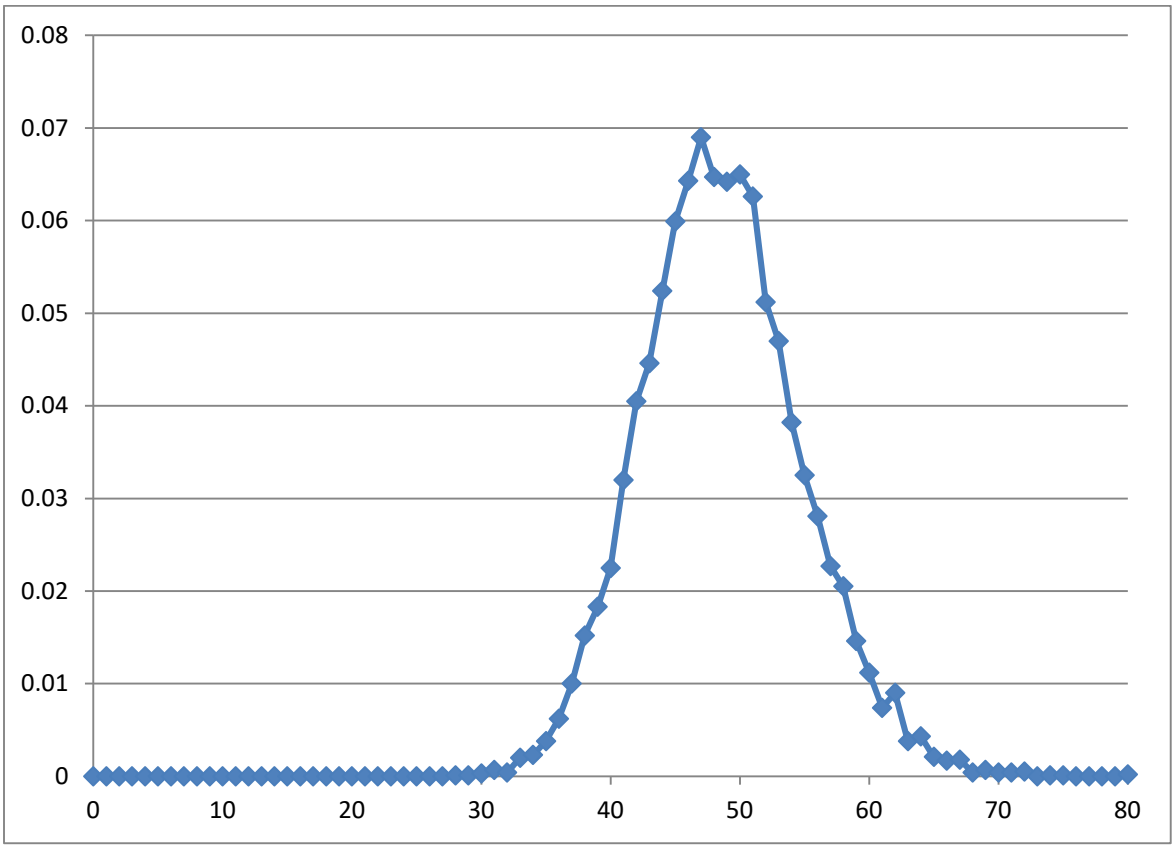
- The significance of the changes will be tested by non-parametric tests (Wilcoxon signed-rank test). Non-parametric test is preferred due to the small sample size and the questionable normality of the data

9.6 Determination of Sample Size

Approximately 10 subjects will be enrolled in the study to receive three vaccinations. The study is not statistically powered to assess the primary or secondary outcomes measures.

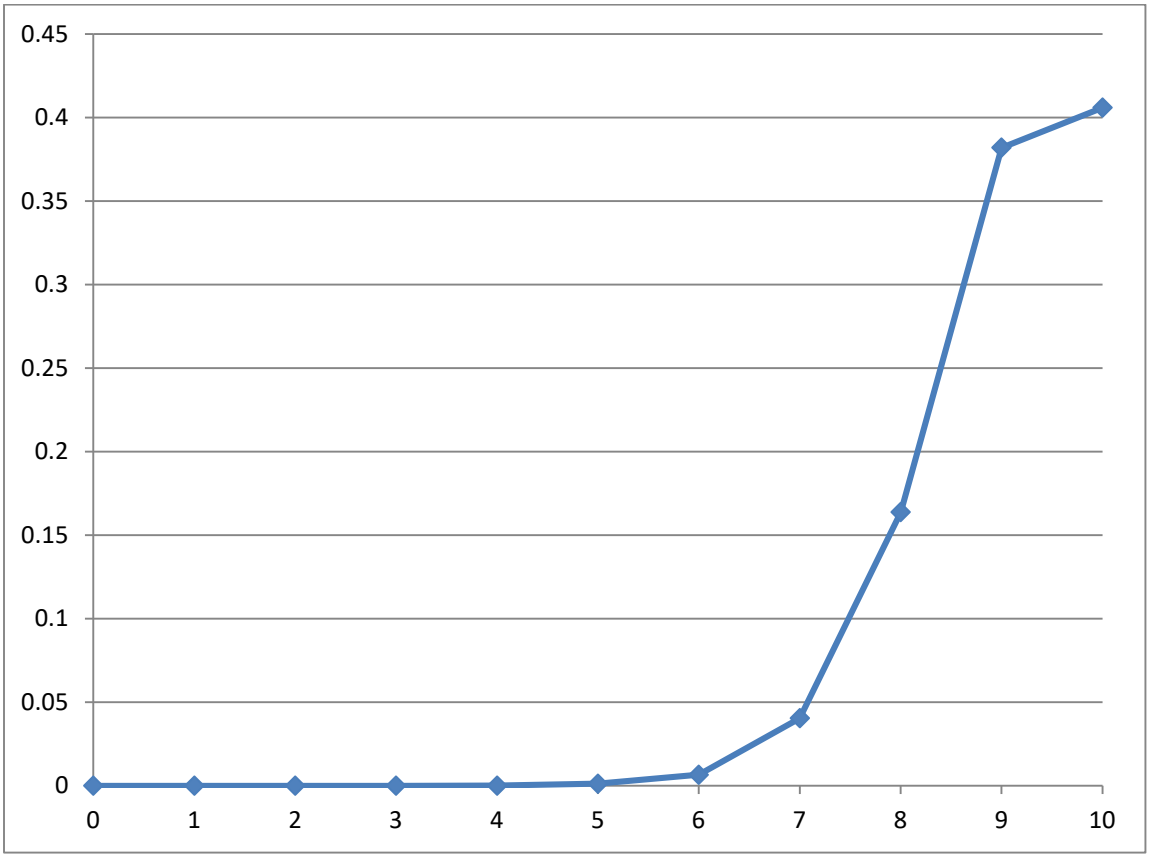
Assuming that the HLA sets from the subjects follow the distribution observed in the HLA sets from the in-house database, at least 39 positive immune responses are expected from 10 subjects. The distribution of the expected number of positive tests is displayed in Figure 4, which is generated from 10,000 simulations. The x-axis shows the number of positive tests, and the y-axis shows the probabilities.

Figure 4. Distribution of the Expected Number of Positive Tests



Based on the simulation, at least 7 subjects are expected to have an immune response against 2 or more cancer antigens with at least 97.5% probability. The expected distribution of probabilities having a given number of subjects with positive immune response for 2 or more antigens is displayed in Figure 5, the x-axis shows the number of subjects with a given probability and the y-axis shows the probability.

Figure 5. Expected Distribution of Probabilities Having a Given Number of Subjects with Positive Immune Response for Two or More Antigens



10 ETHICAL AND LEGAL CONSIDERATIONS

10.1 Compliance Statement

This study will be conducted in accordance with the protocol and with ICH GCP guidelines, as well as all applicable country and regional legal and regulatory requirements. The investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB or IEC prior to the enrollment of any study subjects.

10.2 Ethics Committee and Regulatory Authorities

Before patients participate in this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information will be reviewed and approved/given favorable opinion by the Ethics Committee (EC) and applicable regulatory authorities. The Investigator's Brochure will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval, as described in the Clinical Trial Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(s) approval.

10.3 Informed Consent and Human Subject Protection

Investigators will choose patients for participation while considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients and/or their legally authorized representative must sign an informed consent form before entering into the study according to applicable national and local regulatory requirements and ICH GCP. An assent form may be provided and should be signed by

patients less than 18 years of age. Before use, the informed consent form will be reviewed by the sponsor and approved by the EC and regulatory authority(s), where applicable, (see Section 10.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable national and local regulatory requirements. Patients or their legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients/healthy volunteers or their legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, which has been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the investigator to the subjects who consented to participate in the study.

Four out of ten subjects have already been accrued under the original single-dose Study Design, the first one being accrued in May 2017. These subjects will be asked to sign a new informed consent for multiple dosing.

10.4 Confidentiality

The investigator will comply with the confidentiality policy as described in the Clinical Trial Agreement.

11 ADMINISTRATIVE CONSIDERATION

11.1 Investigator's Responsibilities

The investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable national and local regulatory requirements as described in the Clinical Trial Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

The coordinating investigator will be selected before study start. The coordinating investigator will sign the clinical study report.

11.2 Study Training

The sponsor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the sponsor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor.

11.3 Study Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit the study monitor to visit the study site at appropriate intervals, as described in the Clinical Trial Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

11.4 Safety Monitoring

Accrual, withdrawals from treatment, all toxicities, and AEs will be monitored during the study. Reports should be reviewed every 2 weeks by the safety review team from one week after the study opens until it closes.

If 2 subjects experience a primary safety endpoint (Section 9.4), or 1 subject experiences a ≥Grade 4 AE that is probably or definitely related to study treatment, enrollment will be suspended. Depending on the severity of the AE, study treatment administration to subjects may be terminated, pending a subsequent decision by the study team on how to proceed.

When the last subject reaches Week 12, the safety review team will review all available safety data, including hematology, chemistries, tumor biomarkers, viral load data, and all clinical events.

11.5 Audits

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable national and local regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Trial Agreement. Auditing processes specific to the study will be described in the audit plan.

11.6 Documentation

11.6.1 Case Report Forms and Study Records

The investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include information defined as "source data" (see Section 11.6.3), records detailing the progress of the study for each subject, signed informed consent forms, correspondence with the EC and the study monitor/sponsor, screening information, CRFs, SAE reports (SAERs), laboratory reports (if applicable), and data clarifications requested by the sponsor.

The investigator will comply with the procedures for data recording and reporting. Any corrections to paper study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

The investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in electronic form.

Only authorized study site personnel will record or change data on the CRFs. If data is not entered on the CRFs during the study visit, the data will be recorded on paper, and this documentation will be considered source documentation. Changes to a CRF will require documentation of the reason for each change. An identical (electronic/paper) version of the complete set of CRFs for each subject will remain in the investigator file at the study site in accordance with the data retention policy (see Section 11.6.4).

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (e.g., ICH GCP) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

11.6.2 Direct Access to Source Data, Source Documents, and Study Records

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the IEC, and inspections by applicable regulatory authorities, as described in the Clinical Trial Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Trial Agreement.

11.6.3 Source Data

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical

trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the following: hospital records, medical records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, outcomes reported by subjects, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

No data will be entered directly onto the CRF.

For additional information on study documentation and CRFs, see Section 11.6.1.

11.6.4 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Trial Agreement.

11.7 Non-Compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the subject. In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The sponsor will also ensure the responsible EC and relevant competent authority is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator’s participation. The sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

11.8 Financing and Insurance

The investigator will comply with investigator financing, investigator/sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Trial Agreement.

11.9 Publication Policy

The investigator will comply with the publication policy as described in the Clinical Trial Agreement.

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APPENDIX A. SCHEDULE OF STUDY ASSESSMENTS

Assessment	Period	Screening	Vaccination and Evaluation				
	Visit Number	1	2	3	4	5	6
	End of Week	-3 to -1	0	3	6	9	12
	Day	-21 to -1	1	22 ±2	43 ±2	64±2	85±2
Informed Consent		X					
Inclusion/Exclusion Criteria		X					
ECOG Performance Status		X					
Medical History		X					
Medication History		X					
Concomitant Medications			X	X	X	X	X
Complete Physical Exam		X	X		X		X
Targeted Physical Exam				X		X	
Vital Signs		X	X	X	X	X	X
Vaccine Site Evaluation			X	X	X	X	X
Evaluation of Response to First-line Therapy		X					
Buccal Swab			X				
Vaccine Administration/ 1-hour Observation			X				
Distribute Diary[1]			X				
Collect Diary				X			
Cancer Biopsy/ Tumor Infiltrating Lymphocytes Analysis		X					X
CT and RECIST (irRECIST) Assessment		X			X		X
Hematology & Blood Chemistries		X	X		X		X
Tumor Biomarkers		X	X		X		X
Urinalysis		X	X		X		X
Urine Pregnancy Test		X	X		X		X
Blood Collection for PBMC and Immunogenicity Assays (ELISpot and PHPC)		X	X	X	X	X	X

Abbreviations: ECOG = Eastern Cooperative Oncology Group; CT = computerized tomography
1. The Patient Diary will be used to collect local signs related to the injection sites, physical fatigue, and body temperature

Assessment	Period	Vaccination and Evaluation				
	Visit Number	7	8	9	10	11
	End of Week	13	16	19	22	25
	Day	92 ±2	113 ±2	134 ±2	155 ±2	176 ±2
Informed Consent for additional vaccinations[2]		X				
Concomitant Medications		X	X	X	X	X
Complete Physical Exam		X		X		X
Targeted Physical Exam			X		X	
Vital Signs		X	X	X	X	X
Vaccine Site Evaluation		X	X	X	X	X
Vaccine Administration/ 1-hour Observation		X				
Distribute Diary[1]		X				
Collect Diary			X			
Cancer Biopsy/ Tumor Infiltrating Lymphocytes Analysis						X
CT and RECIST (irRECIST) Assessment				X		X
Hematology & Blood Chemistries				X		X
Tumor Biomarkers				X		X
Urinalysis				X		X
Urine Pregnancy Test				X		X
Blood Collection for PBMC and Immunogenicity Assays (ELISpot and PHPC)			X	X	X	X

Abbreviations: CT = computerized tomography

1. The Patient Diary will be used to collect local signs related to the injection sites, physical fatigue, and body temperature
2. Only for those subjects who had originally signed an Informed Consent Form for a single vaccination

Assessment	Period	Vaccination and Evaluation				
	Visit Number	12	13	14	15	16
	End of Week	26	29	32	35	38
	Day	183 ±2	204 ±2	225 ±2	246 ±2	267 ±2
Concomitant Medications		X	X	X	X	X
Complete Physical Exam		X		X		X
Targeted Physical Exam			X		X	
Vital Signs		X	X	X	X	X
Vaccine Site Evaluation		X	X	X	X	X
Vaccine Administration/ 1-hour Observation		X				
Distribute Diary[1]		X				
Collect Diary			X			
Cancer Biopsy/ Tumor Infiltrating Lymphocytes Analysis						X
CT and RECIST (irRECIST) Assessment				X		X
Hematology & Blood Chemistries				X		X
Tumor Biomarkers				X		X
Urinalysis				X		X
Urine Pregnancy Test				X		X
Blood Collection for PBMC and Immunogenicity Assays (ELISpot and PHPC)			X	X	X	X

Abbreviations: CT = computerized tomography
1. The Patient Diary will be used to collect local signs related to the injection sites, physical fatigue, and body temperature

Note: At the end of the follow up period (that is 12 weeks after each vaccination), ideally one week rest period should be observed before the next vaccination, as described in the above SoA. However, up to 1 month rest period is allowed.

APPENDIX B. THE WORLD ALLERGY ORGANIZATION SUBCUTANEOUS IMMUNOTHERAPY SYSTEMIC REACTION GRADING SYSTEM

See attached Article (13 pages) by Cox L. et al