Investigational Product: IMU-131
Protocol Identifier: IMU.ACS.001
Protocol Version: Protocol Global Amendment #5, 27 September 2023

HERIZON: A PHASE 1B/2 OPEN-LABEL STUDY OF IMU-131 **HER**2/NEU PEPTIDE VACCINE PLUS STANDARD OF CARE CHEMOTHERAPY WITH RANDOM**IZ**ATI**ON** IN PHASE 2 IN PATIENTS WITH HER2/NEU OVEREXPRESSING METASTATIC OR ADVANCED ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

Compound:	IMU-131
Compound Name:	HER-Vaxx
Protocol Number:	IMU.ACS.001
Sponsor:	Imugene Limited Suite 12.01, Level 12 4-6 Bligh Street SYDNEY NSW 2000 Australia
Amendment:	5
Amendment Date:	27 September 2023

Approver's Name and Title: [redacted] **Signature:** [redacted] **Date:** 12-Oct-2023 | 22:07 AEDT

The name, title, address and telephone number(s) of the Sponsor's medical experts for the trial are documented in the study contact list located in the study coordinator's manual.

PROTOCOL ACCEPTANCE FORM

HERIZON: A PHASE 1B/2 OPEN-LABEL STUDY OF IMU-131 **HER**2/NEU PEPTIDE VACCINE PLUS STANDARD OF CARE CHEMOTHERAPY WITH RANDOM**IZ**ATI**ON** IN PHASE 2 IN PATIENTS WITH HER2/NEU OVEREXPRESSING METASTATIC OR ADVANCED ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

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Sponsor:	**Imugene Limited** **Suite 12.01, Level 12** **4-6 Bligh Street** **SYDNEY NSW 2000** **Australia**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your investigator site file and return a copy to your local study monitor.

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original protocol	6 April 2016	N/A
Thailand specific protocol addenda #1	2 February 2017	Additional Exclusion Criteria to exclude patients with diphtheria toxoid hypersensitivity. See Appendix 4.
Taiwan specific protocol addenda #1	13 March 2017	To confirm the sequential enrolment of Taiwanese patients - at least 14 days apart in the first dose cohort. To increase the observation time for Taiwan patients dosed in the study to 6 hours post first injection. See Appendix 5.
Global Amendment #1	2 August, 2017	Update Sponsor address Modify Inc#6 to allow inclusion of patients with IHC HER2++ expression. Modify Inc#8 to allow inclusion of patients without measurable disease. Include justification for 2 injections before start of chemotherapy. Separate heading for DLT definition. Update post-study SAE reporting period to coincide with 28-day post-study AE reporting period Include re-screening process [redacted] for vaccine and adjuvant. Remove Appendix 2 details and indicate moved to study file. Include Thailand specific addenda 2 Feb 17 Include Taiwan specific addenda 13 Mar 17 Various typographical and grammatical corrections. Update references.
Global Amendment #2	23 November 2018	Update introduction with Phase 1b results Update with detail for Phase 2 part

Document	Version Date	Summary of Changes
		of the protocol Re-arrange order of sections Various typographical and grammatical corrections Update references
Global Amendment #3	17 February 2021	Modify title, change principal physician Modify number patients to be enrolled and number of events required to meet endpoints Modify exploratory endpoint analysis Add optional post-progression tumor sample Update protocol to align with notes to file including correction of tumor 'grade' to 'stage', addition of telemedicine process, clarification of AE/SAE reporting for ineligible and re-screened patients.
Global Amendment #4	12 August 2021	Addition of Phase 2 Extension study to examine safety and efficacy of higher doses of IMU-131. Update to Phase 2 statistical section to align protocol and SAP. Addition of references, and grammatical corrections.
Global Amendment #5	TBA	Clarification of end of study Modified contraception and pregnancy timelines. Removed reference to arms from Phase 2 Extension objectives and endpoints Addition of future use of samples Removed Moldova as participating country in Phase 2 Extension Updated Sponsor address Updated DLT criteria to be consistent throughout Other formatting and administrative changes

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LIST OF ABBREVIATIONS

°C	degree Celsius
µg	microgram
µL	microliter
5-FU	5-fluorouracil
ACS	Advanced cancer of the stomach
ADCC	Antibody-dependent cellular cytotoxicity
AE(s)	Adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
B cell	B lymphocyte
BDISH	brightfield double in situ hybridization
BHCG	beta-human chorionic gonadotrophin
BSA	Body Surface Area
BUN	blood urea nitrogen
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CEA	Carcinoembryonic antigen
CISH	chromogenic in situ hybridization
CIV	continuous intravenous infusion
CR	Complete Response
CRC	Cohort Review Committee
CRF	Case report form
CRO	Contract research organization-
CRP	C-reactive protein
CT	Computed tomography
CTCAE	National Cancer Institute's Common Toxicity Criteria for Adverse Events
CTS	Change in Tumor Size
DCR	Disease Control Rate
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECD	extracellular Domain
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EGF	epithelial growth factor
ER	Emergency Room
EVAL	Evaluable Set
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FISH	Fluorescent in situ hybridization
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GGT	gamma glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2/neu	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular(ly)
IMU	Imugene Limited, Australia
IMU-131	Investigational product consisting of P467-CRM in Montanide adjuvant
IRB/IEC	Institutional review board/independent ethics committee
ISA	Industry Standard Architecture
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous(ly)
IxRS	Interactive Voice or Web Response System
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LTM	Long-term Maintenance
LVEF	Left ventricular ejection fraction
m	mass

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mm	millimeter
MUGA	Multiple gated acquisition (scan)
N	number
NCCN	US National Comprehensive Cancer Network®
NCI	National Cancer Institute
NICE	National Institute for Health and Care Guidance
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PD	Progressive Disease
PEV6C	First generation formulation of IMU-131
PFS	Progression Free Survival
PI	Principal Investigator
PP	Per-Protocol
PR	Partial Response
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
S.A.	société anonyme
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SD	Stable Disease
SOC	standard of care
T cell	T lymphocyte
TEAEs	Treatment-emergent Adverse Events
ToGA	Trastuzumab for Gastric Cancer
TTP	Time to Progression

ULN	Upper limit of normal
WBC	White blood cell

CLINICAL PROTOCOL SYNOPSIS

Study Number and Title	**IMU.ACS.001** HERIZON: A Phase 1b/2 Open-label Study of IMU-131 **HER**2/neu Peptide Vaccine Plus Standard of Care Chemotherapy with random**iz**ati**on** in Phase 2 in Patients with HER2/neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction
Sponsor	Imugene Limited
Indication	HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or gastroesophageal junction, also known as Advanced Cancer of the Stomach (ACS).
Number of patients	Multicenter with a maximum of 18 patients enrolled in Phase 1b and approximately 36 patients enrolled in Phase 2. Phase 2 Extension will enroll up to 20 patients: 3-9 patients during dose escalation with either dose cohort expanded up to 10 patients.
Clinical Phase	The Phase 1b study is an open-label, multicenter dose escalation study designed to assess the safety, tolerability, immunogenicity and recommended phase 2 dose (RP2D) of IMU-131. The RP2D will be evaluated in the dose expansion Phase 2 study which will be submitted as an amendment to this Phase 1b/2 protocol during the conduct of the Phase 1b study. Phase 2 is an open-label, randomized, multicenter study designed to assess the clinical activity, immunogenicity, safety and tolerability of IMU-131. The length of Phase 2 will be approximately 30 months: 22 months' recruitment and an estimated 8 months' follow-up from completion of recruitment to realization of the required number of deaths. It is anticipated that an additional 3 months will be required to complete the analyses following realization of the last required death. Phase 2 Extension: dose escalation in Phase 2 is an open-label, multicenter, single arm study to assess safety, tolerability, immunogenicity, and preferred dose for further development of IMU-131. The duration of Phase 2 dose escalation study will be approximately 24 months: 15 months for recruitment and approximately 12 months on study. Once the last enrolled patient completes the end of treatment visit, the Sponsor may close the study.
Rationale	Almost one million new cases of gastric cancer were estimated to have occurred worldwide in 2012, making it the fifth most common malignancy in the world and the third leading cause of cancer death in both sexes worldwide. HER2/neu is overexpressed in 15% to 25% of patients with gastric cancer and is associated with a worse prognosis,

	more aggressive disease, and poorer survival. While the addition of a monoclonal antibody against HER2/neu (trastuzumab) to cisplatin and either 5-fluorouracil (FU) or capecitabine chemotherapy has shown significant benefit over chemotherapy alone, alternative treatments are needed because trastuzumab is not available everywhere, is costly, and is associated with potentially serious side effects. IMU-131 is a single peptide structure composed of 3 individual B-cell epitope peptide sequences selected from HER2/neu structure. Polyclonal antibodies against IMU-131 peptides bind three separate regions of the HER2 receptor and also to the dimerization loop of the HER2 receptor, preventing dimerization, which in turn inhibits intracellular signaling. This blockade of the HER2 signaling pathways is thought to be substantially greater than that with trastuzumab alone. Safety and immunogenicity of the 3 peptides have been shown in Phase 1 testing of an earlier formulation of IMU-131. The shelf stability of the Phase 1 vaccine was not optimal and hence the formulation was adjusted for IMU- 131. The three B-cell epitope peptides (P4, P6 and P7) were combined in a specific order resulting in a single fusion peptide of 49 amino acids in length (P467). This new formulation of IMU-131 has extended stability and improved immunogenicity compared to the formulation used previously. The new vaccine IMU-131 produces a stronger and more rapid polyclonal antibody response and is efficient to manufacture compared with previous formulations. Based on these three known epitopes (P4, P6 and P7), we developed a single peptide antigen (P467), which allows simplification of the manufacturing process. First, only one batch of peptide needs to be produced and qualified. Second, compatibility problems during the formulation process due to different physico-chemical properties of different peptides are circumvented. Third, equal dosing of the three epitopes in the formulation is inherently guaranteed with a single peptide. It is hypothesized that administration of IMU-131 in addition to chemotherapy will prolong survival and may delay tumor progression and/or reduce tumor burden in patients with HER2/neu overexpressing gastric or gastroesophageal junction (GEJ) adenocarcinoma. This phase1b/2 protocol is made up of 2 components. The first component is the Phase 1b study, which is wholly detailed in this protocol. The second component consists of the Phase 2 evaluation of clinical activity of IMU-131 which will be submitted as an amendment to this phase 1b/2 protocol after initiation of the Phase 1b study. The Phase 1b study aims to determine the safety and tolerability of IMU-131 and identify the Recommended Phase 2 Dose (RP2D) of IMU-131 in combination with chemotherapy in HER2/neu overexpressing ACS to carry into the Phase 2 dose expansion study. The Phase 2 component will be submitted as an amendment and will be initiated following completion of Phase 1b. Phase 2 will be designed to further characterize the safety and to explore clinical activity of IMU-131 in combination with

	chemotherapy in HER2/neu overexpressing ACS. Phase 2 Extension Further increasing the dose of IMU-131 is supported by safe administration based on existing clinical data with no IMU-131 related safety signals, dose limiting toxicities, or SUSARs reported during either the Phase 1b or Phase 2 study. The selection of the 50µg dose for Phase 2 was based on Her2/neu antibody development and response compared to the lower dose levels studied and not on any IMU-131 related toxicity. To explore further treatment options for different treatment lines of GC/GEJ cancer, in particular after progression on trastuzumab, a higher dose than currently used in Phase 2 is considered a potentially stronger treatment option. Safety data from the 36 patient Phase 2 study supports dose escalation above 50µg IMU-131 because no IMU-131 related safety signals, dose limiting toxicities, or SUSARs have been reported. Dose escalation in Phase 2 will have 2 dose cohorts, 100µg and 200µg IMU-131, to further characterize the safety, clinical activity, and immunogenicity of IMU-131 with SOC chemotherapy as first-line treatment for HER2/neu overexpressing metastatic/advanced gastric or GEJ cancer.
Objectives	Objectives of Phase 1b study: • To evaluate the safety and tolerability of IMU-131 administered intramuscularly (IM) and initiated 14 days (+/- 1 day) prior to cisplatin, intravenous (IV) and either 5-FU, IV or capecitabine, oral chemotherapy in patients with HER2/neu overexpressing ACS; • To identify the Recommended Phase 2 Dose of IMU-131, administered IM and initiated 14 days (+/- 1 day) prior to chemotherapy in patients with HER2/neu overexpressing ACS for evaluation in Phase 2. Exploratory objectives of Phase 1b study: • Humoral and tumoral immunogenicity data will be used to further explore the mechanism of action for anti-tumor effects of IMU-131; • Radiographic data will be used for an exploratory determination of Response Rate. Phase 2 Primary Objective: • To evaluate the clinical efficacy of IMU-131 plus chemotherapy compared to chemotherapy alone based on overall survival (OS). Phase 2 Secondary Objectives: • To evaluate other efficacy measures of IMU-131 plus chemotherapy compared to chemotherapy alone including

	progression-free survival (PFS), time to progression (TTP), disease control rate (DCR), objective response rate (ORR), duration of objective response (DOR) and change in tumor size (CTS) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) for the progression evaluation of radiographic data. • To evaluate the safety profile of IMU-131 plus chemotherapy compared to chemotherapy alone. <u>Phase 2 Exploratory Objectives</u>: • To evaluate humoral and cellular immunogenicity data of IMU-131 plus chemotherapy compared to chemotherapy alone including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells. • To evaluate the arm-specific associations between clinical outcome, intra-tumor T cells, regulatory and effector T and B cells, and serum and biochemical markers of tumor progression. • To evaluate arm-specific associations between clinical outcome and HER2 and PD-L1 expression in tumor tissue. • To evaluate inhibition of in-vitro tumor cell growth and intra-cellular signaling processes by Her-2-specific antibodies (IgG) <u>Phase 2 Dose Escalation Primary Objective:</u> • To evaluate the safety and tolerability of 100µg and 200µg of IMU-131 in combination with chemotherapy. <u>Phase 2 Dose Escalation Secondary Objectives:</u> • To evaluate efficacy of IMU-131 plus chemotherapy including OS, PFS, TTP, ORR, DOR, DCR, and CTS according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) for the progression evaluation of radiographic data. <u>Phase 2 Dose Escalation Exploratory Objectives</u>: • To evaluate humoral and cellular immunogenicity data of IMU-131 plus chemotherapy compared to chemotherapy alone including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells. • To evaluate associations between clinical outcome, intra-tumor T cells, regulatory and effector T and B cells, and serum and biochemical markers of tumor progression. • To evaluate associations between clinical outcome and HER2 and PD-L1 expression in tumor tissue. • To evaluate inhibition of in-vitro tumor cell growth and intra-

	cellular signaling processes by Her-2-specific antibodies (IgG).
Endpoints	Phase 1b study endpoints: • The safety and tolerability of IMU-131 will be evaluated by adverse events (AEs) and laboratory measurements. AEs and laboratory abnormalities will be graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03; • The recommended phase 2 dose will be evaluated by safety/tolerability and immunogenicity data for IMU-131 (P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) titers). Phase 1b study exploratory endpoints: • Humoral and cellular immunogenicity data will include P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) in serum samples and vaccine-specific cytokine levels as well as analysis of regulatory and effector T and B cells taken across study visits. As prediction markers of tumor progression initial evaluation (prior first vaccination) of intra-tumor T cells and regulatory cells in tumor biopsies will be performed, when these tests are available at the hospital pathology laboratory. • Radiographic data will be analyzed descriptively to explore Response Rate and provide information for sample size calculation for the Phase 2 study. Phase 2 Primary Efficacy Endpoint: • OS measured from randomization to death due to any cause. Phase 2 Secondary Efficacy Endpoints: • PFS measured from randomization to date of earliest progressive disease (PD) based on blinded central review according to RECIST 1.1 criteria, or to date of death from any cause. • TTP measured from randomization to date of earliest PD based on blinded central review according to RECIST 1.1 criteria. • DCR measured from randomization as the proportion of patients achieving a confirmed best overall response of complete response (CR), partial response (PR) or stable disease (SD) based on blinded central review according to RECIST 1.1 criteria. • ORR measured from randomization as the proportion of patients achieving a confirmed best overall response of CR or PR based on blinded central review according to RECIST 1.1 criteria. • DOR measured from when earliest CR or PR is observed to PD or death due to any cause based on blinded central review according to RECIST 1.1 criteria. • Percentage CTS measured from randomization as the sum of

	diameters based on blinded central review according to RECIST 1.1 criteria. Phase 2 Exploratory Endpoints: • Values and changes from randomization in humoral and cellular immunogenicity data including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells. • Values and changes from randomization in serum and biochemical markers of tumor progression. • Values and changes from randomization in Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth. • Values and changes from randomization in intra-tumor T cells and biochemical markers from pre- and post- treatment tumor biopsies. Phase 2 Safety Endpoints: • Incidence of treatment-emergent adverse events (TEAEs), Grade 3 / 4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study treatment discontinuation. • Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities. • Changes and shifts from randomization in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters. • Change from randomization in ECOG performance grade. • Concomitant medication use. • Treatment compliance. Phase 2 Dose Escalation Primary Endpoint: • The safety and tolerability of IMU-131 will be evaluated by adverse events (AEs) and laboratory measurements. AEs and laboratory abnormalities will be graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 including: - Incidence of treatment-emergent adverse events (TEAEs), Grade 3 / 4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study treatment discontinuation. - Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities. - Changes and shifts in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters. Phase 2 Dose Escalation Secondary Endpoints: • OS measured from enrollment to death due to any cause. • PFS measured from enrollment to date of earliest progressive

	disease (PD) based on Investigator disease assessment according to RECIST 1.1 criteria, or to date of death from any cause. • TTP measured from enrollment to date of earliest PD based on Investigator disease assessment according to RECIST 1.1 criteria. • ORR measured from enrollment as the proportion of patients achieving a confirmed best overall response of CR or PR based on Investigator disease assessment according to RECIST 1.1 criteria. • DOR measured from enrollment to when earliest CR or PR is observed to PD or death due to any cause based on Investigator disease assessment according to RECIST 1.1 criteria. • DCR measured from enrollment as the proportion of patients achieving a confirmed best overall response of complete response (CR), partial response (PR) or stable disease (SD) based on Investigator disease assessment according to RECIST 1.1 criteria. • Percentage CTS measured from enrollment as the sum of diameters based on Investigator disease assessment according to RECIST 1.1 criteria. <u>Phase 2 Dose Escalation Exploratory Endpoints</u>: • Values and changes from enrollment in humoral and cellular immunogenicity data including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells. • Values and changes from enrollment in serum and biochemical markers of tumor progression. • Values and changes from enrollment in Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth. • Values and changes from enrollment in intra-tumor T cells and biochemical markers from pre- and post- treatment tumor biopsies.
Study Design	This protocol has a 2-part design. <u>Part 1 consists of Phase 1b: Dose Escalation</u> Phase 1b is an open-label, single arm, dose escalation study to evaluate safety, tolerability and immunogenicity and to assess the RP2D of IMU-131 initiated 14 days prior to the start of chemotherapy. All patients entering the Phase 1b study will receive IMU-131 and chemotherapy. RP2D is defined as the dose resulting in the best safety/tolerability and immunology results and will be determined after all dose cohorts have completed Day 56 of the study and an interim analysis of the Phase 1b data has been conducted by the Cohort Review Committee (CRC). <u>Phase 1b Long Term Maintenance (LTM)</u> Within Phase 1b there is provision for patients to continue on IMU-131 as long-term maintenance. Patients completing the Day 56/End of

	Treatment Visit for Phase 1b will be maintained on booster doses of IMU-131 starting from Day 98. Duration of treatment in Phase 1b Each patient will be administered 3 injections of IMU-131 (P467-CRM197-Montanide emulsion), at a single dose level on Days 0, 14, and 35, accompanied by chemotherapy cycles every 21 days starting from Day 14. Chemotherapy will be ceased by the investigator when clinically indicated for the care of the patient. Patients will be discontinued from the study and cease IMU-131 vaccinations when there is documented evidence of disease progression according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) or if unacceptable toxicity occurs (see Section 6.5 Patient Withdrawal for complete discontinuation criteria). Part 2 consists of Phase 2: Evaluation of exploratory clinical activity of IMU-131 Phase 2 will enroll approximately 36 patients and be conducted in the same centers with the addition of new centers, as required, to fulfill recruitment. Phase 2 will have similar inclusion/exclusion criteria and be conducted according to a similar schedule of events and study procedures. During conduct of the Phase 1b study and prior to the start of Phase 2, an amendment to the current protocol will be submitted for ethical and regulatory review. The Phase 2 evaluation of clinical activity of IMU-131 will be initiated after approval of Phase 2 and upon completion of Phase 1b (all cohorts completed through Day 56 and selection of a RP2D of IMU-131). Phase 2 is an open-label randomized comparison of IMU-131 plus standard of care chemotherapy versus standard of care chemotherapy alone. Patients will be randomly assigned to either 'IMU-131 plus chemotherapy' or 'chemotherapy alone' groups. Treatment for both groups will begin at the Baseline/Day 0 visit. The IMU-131 plus chemotherapy group will receive vaccination of IMU-131 at Baseline/Day 0, Day 14, Day 35, Day 77, Day 140 and then every 63 days until disease progression. Both the IMU-131 plus chemotherapy group and the chemotherapy alone group will receive chemotherapy starting at the Baseline/Day 0 Visit and then every 21 days for a maximum of 6 cycles as clinically indicated or until disease progression, whichever occurs sooner. Phase 2 Extension Dose escalation during Phase 2 is an open-label, multicenter, single arm dose escalation study with the same inclusion/exclusion criteria as Phase 2 and the same schedule of assessments (SoA) as Phase 2 IMU-131+chemotherapy arm. Patients will no longer be followed for post treatment follow up. The safety of each dose will be assessed by CRC after at least 3 patients have 3 doses of IMU-131 and one cycle of chemotherapy and have completed the 35 day DLT window. Two dose cohorts, consisting of 100µg and 200µg dose levels of IMU-131, will

	further characterize the safety, immunogenicity, and clinical activity of IMU-131 in combination with chemotherapy. The Sponsor may close the study once the last patient completes the end of treatment visit.
Population	The phase1b/2 protocol is a multicenter study. Phase 1b will enroll up to a maximum of 18 patients, Phase 2 will enroll approximately 36 patients, and Phase 2 dose escalation will enroll up to 20 patients diagnosed with advanced/metastatic, HER2/neu overexpressing, gastric or GEJ adenocarcinoma who meet all inclusion criteria and no exclusion criteria. The Phase 2 extension dose escalation study will be conducted at sites in Georgia, Ukraine, and Serbia.
Phase 2 Randomization and Blinding	In Phase 2, patients who are determined to be eligible for the study will be randomized on their Baseline/Day 0 Visit. Patients will be allocated to receive IMU-131 plus chemotherapy or chemotherapy only in a 1:1 ratio. Randomization will be performed centrally and stratified by tumor stage at screening (III vs IV). Patients will be randomized into this open-label study using an Interactive Voice or Web Response System (IxRS). The central radiography review will be blinded. The rules describing the distribution of data and results will be documented prior to study commencement. Phase 2 Extension: dose escalation in Phase 2 is open label and non-randomized with patients entering the study sequentially according to the dose level being studied.
Sample size and sample size determination	[redacted]

	 PFS will be assessed as a secondary outcome with an analysis following 24 evaluable progression events coded using RESIST 1.1 with patients not having a progression being censored at the time of last evaluation for progression or counted as a progression event if death is within 42 days of last evaluation for progression. Assumptions of accrual time, loss to follow-up, and pooled event rate (both arms combined) used in the sample size calculations may be monitored. The number of patients enrolled, and duration of enrolment and follow-up may be adjusted to achieve the planned number of events at the time of the final analysis of the primary endpoint. Phase 2 Extension: Phase 2 dose escalation will enroll up to 20 patients. No formal statistical calculation of sample size will be used for the Phase 2 dose escalation. The sample size is empirical and based on a standard 3+3 dose escalation design with expansion of up to 10 patients per dose escalation cohort.
Safety Monitoring	**<u>Phase 1b:</u>** <u>Cohort Review Committee (CRC)</u> Prior to enrollment of patients into the Phase 1b study, a CRC, comprising relevant site investigators, the Medical Monitor, and Sponsor representatives, will oversee safety, cohort evaluation and dose-escalation for the study. A formal charter which will establish the rules, meeting frequency and scope of responsibilities of the CRC will be established for the conduct of the CRC. <u>Dose Escalation within Phase 1b</u> There will be up to 6 patients in each cohort in Phase 1b. The CRC will review data from one complete cycle of chemotherapy (including 3 doses

	of IMU-131, on Days 0, 14, and 35) for at least 3 patients in a dose cohort to authorize dose escalation. A staggered enrollment will be used for patient safety, whereby a dose cohort must be completed and reviewed by the CRC before further recruitment. The decision whether to escalate to the next dose cohort will be made by the CRC when at least 3 patients in the current dose cohort have completed chemotherapy cycle 1 (35 days of the study, including 3 doses of IMU-131 on Days 0,14 and 35). Phase 1b dose escalation will involve 3 dose levels of IMU-131 with a standard 3+3 scheme for determination of safety prior to dose escalation. Patients will receive 3 doses of IMU-131 (Days 0, 14 and 35) with chemotherapy being initiated 14 days after the first dose of IMU-131 with evaluation occurring after the first 21-day cycle of chemotherapy and before opening the enrollment to the next higher dose cohort. Dose Escalation Decision Rules • If 0 out of 3 patients with treatment related dose-limiting toxicity (DLT) at a given IMU-131 dose level, enter 3 patients at the next dose level (DLT: a drug-related Grade 3 toxicity that cannot be resolved to a Grade 1 with appropriate therapy within 2 weeks, or a Grade 4 or greater toxicity graded by CTCAE v4.03, related to the IMU-131 vaccine). • If ≥2 of 3 patients with treatment related DLT at a given dose level, dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose • If 1 out of 3 patients with treatment related DLT at a given dose level, enter at least 3 more patients at this dose level. If 0 of these 3 patients experience treatment related DLT, proceed to the next dose level. If 1 or more of this group suffer treatment related DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients may be entered at a dose between the current dose and the next lowest dose level, the exact dose of which will be determined by the CRC. **Phase 2** The Independent Data Monitoring Committee (IDMC) will be scheduled to meet after 8, 16 and 24 progression events occur and at intervals no less than once per year. Further details of the IDMC meetings and review procedures will be contained in the IDMC charter. **Phase 2 Extension** Dose Escalation within Phase 2 Between 3 - 6 patients will be enrolled in each Phase 2 dose escalation

	cohort for safety evaluation by CRC prior to next dose being opened to enrollment. The CRC will review data from one complete cycle of chemotherapy and 3 doses of IMU-131, for at least 3 patients in a dose cohort to authorize dose escalation. The DLT window is 35 days. Dose escalation in Phase 2 will start at 100µg IMU-131, within a standard 3 + 3 scheme for determination of safety prior to opening enrollment to the 200µg IMU-131 dose cohort. A dose cohort must be reviewed by CRC for DLTs according to dose escalation decision rules before opening the next dosed cohort. Either the 100µg or 200µg dose escalation cohort may be expanded up to 10 patients after CRC clearance of the 35-day DLT period. <u>Phase 2 Dose-limiting Toxicity Definition</u> A dose limiting toxicity (DLT) is defined as an IMU-131-related Grade 3 toxicity that cannot be resolved to a Grade 1 with appropriate therapy within 2 weeks, or a Grade 4 or greater toxicity graded by CTCAE v5.0, related to the IMU-131 vaccine. In addition, after enrollment in Phase 2 dose escalation begins, the CRC will meet by teleconference as soon as feasible after any of the following occur to determine if the criteria for dose limiting toxicity (DLT) has been met: • One or more patients experience a serious adverse reaction assessed as related to the vaccine by the investigator. • One or more patients experience anaphylaxis. <u>Phase 2 Dose Escalation Decision Rules</u> Dose escalation within Phase 2 will follow the same dose escalation rules and CRC review process as Phase 1b. • A dose limiting toxicity (DLT) is defined as an IMU-131-related Grade 3 toxicity that cannot be resolved to a Grade 1 with appropriate therapy within 2 weeks, or a Grade 4 or greater toxicity graded by CTCAE v5.0, related to the IMU-131 vaccine. • In addition, after enrollment in Phase 2 dose escalation begins, the CRC will meet by teleconference as soon as feasible after any of the following occur to determine if the criteria for dose limiting toxicity (DLT) has been met: • One or more patients experience a serious adverse reaction assessed as related to the vaccine by the investigator. • One or more patients experience anaphylaxis. <u>Phase 2 Dose Escalation Decision Rules</u> Dose escalation within Phase 2 will follow the same dose escalation rules and CRC review process as Phase 1b.

Statistical Analysis	[redacted]
Inclusion Criteria	Patients must meet all the following inclusion criteria to be eligible for enrollment into the study: 1. Patient has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines; 2. Age ≥ 20 years old; 3. Life expectancy of at least 12 weeks; 4. **Phase 1b:** No prior chemotherapy or radiotherapy for advanced gastric or GEJ cancer within 6 months prior to Day 0; **Phase 2/Phase 2 Extension:** No prior chemotherapy or radiotherapy for advanced gastric or GEJ cancer within 3 months prior to Day 0;

	5. Metastatic gastric or GEJ adenocarcinoma, or locally advanced disease not amenable to surgical resection; 6. HER2/neu overexpression (3+ by immunohistochemistry (IHC) or if IHC 2+ confirmed by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic in situ hybridization [CISH]). Patients with IHC 2+ expression without confirmation of overexpression by fluorescent in situ hybridization [FISH], BDISH or chromogenic in situ hybridization [CISH]) may be included in Phase 1b with agreement of Imugene Limited; 7. **Phase 1b:** ECOG performance status 0–1; **Phase 2/Phase 2 Extension:** ECOG performance status 0–2; 8. At least one measurable lesion as defined by RECIST 1.1 criteria. Patients with non-measurable lesions may be included in Phase1b with agreement of Imugene Limited; 9. Adequate left ventricular ejection function at baseline, defined as LVEF > 50% by echocardiogram or MUGA scan (Multi Gated Acquisition Scan); 10. Adequate hematologic function: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin ≥ 9 g/dL; 11. Adequate liver function evidenced by bilirubin ≤ 1.5 x laboratory upper limit of normal [ULN], and ALT and AST ≤ 3 x laboratory ULN if no liver involvement or ALT and AST ≤ 5 times laboratory ULN with liver involvement; 12. Adequate renal function (creatinine ≤ 1.5 x laboratory ULN); 13. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. 14. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days following chemotherapy or 180 days after the last dose of IMU-131 (see Section 4.3 for details). A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
Exclusion Criteria	Patients presenting with any of the following will not be included in the study: 1. Previous treatment with trastuzumab or any other HER2/neu targeting antibody or agent; 2. Continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 4 weeks prior to first dose of study treatment.

	Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted in the absence of active auto-immune disease; 3. Prior organ transplant; 4. **Phase 1b:** Patient not considered a candidate for 5-FU, capecitabine, or cisplatin chemotherapy; **Phase 2/Phase 2 Extension:** Patient not considered a candidate for 5-FU, capecitabine, cisplatin or oxaliplatin chemotherapy; 5. History of documented congestive heart failure; angina pectoris requiring antianginal medication; evidence of transmural infarction on ECG; poorly controlled hypertension; clinically significant valvular heart disease; high risk uncontrolled arrhythmias; or New York Heart Association (NYHA) class II heart disease; 6. If on warfarin (Coumadin®) or other vitamin K antagonists; 7. Concurrent active malignancy except for adequately controlled limited basal cell carcinoma of the skin; 8. Peripheral neuropathy or hearing loss of NCI CTCAE Grade $\geq$ 2; 9. History of uncontrolled seizures, central nervous disorders or psychiatric disability judged by the investigator to be clinically significant and precluding informed consent, participation in the study, or adversely affecting compliance to study drugs; 10. Active infection requiring IV antibiotics; 11. Positive for human immunodeficiency virus (HIV) (HIV 1/2 antibodies) or active hepatitis B (HBsAg reactive) or active hepatitis C (HCV ribonucleic acid [RNA] qualitative) infection; 12. Pregnant or lactating females; 13. Major surgery within 4 weeks prior to study entry. Minor surgery (excluding diagnostic biopsy) within 1 week prior to study entry; 14. Has received a live-virus vaccination within 4 weeks of first study vaccination. Seasonal flu vaccines that do not contain live virus are permitted; 15. Current or recent (within 4 weeks of first IMU-131 vaccination) treatment with another investigational drug or participation in another investigational study. 16. **Phase 2/Phase 2 Extension:** Patients with a known diphtheria toxoid hypersensitivity.
Study drugs/Dosage forms/Routes	The investigational product, IMU-131, will be supplied as P467-CRM197 (aqueous phase vaccine) and Montanide ISA 51 VG (adjuvant) in separate boxes. Each box of P467-CRM197 contains 1 vial of 200 µg aqueous phase vaccine in 1 mL PBS buffer, two vial adapters, two luer-lock syringes, one dosing syringe and needle and one I connector. Each box of

	Montanide contains a single 3 mL vial of Montanide ISA 51 VG. IMU-131 vaccine for IM administration to be prepared by the study pharmacist or study site personal on the day of injection [redacted] In Phase 1b, the IMU-131 vaccine will be administered IM into the deltoid region of the upper arm with a 0.60 x 25 mm 23G needle on Days 0, 14 and 35. In Phase 2, the IMU-131 vaccine will be administered IM into the deltoid region of the upper arm with a 0.60 x 25 mm 23G needle on Days 0, 14, 35, 77, 140 and then every 63 days. In Phase 2 Extension, the IMU-131 vaccine will be administered at doses of either 100µg or 200µg IM into the deltoid region of the upper arm with a 25-38mm (1-1.5 inches), 21-23G needle on Days 0, 14, 35, 77, 140 and then every 63 days. Storage conditions for Investigational Product: a) IMU-131 in aqueous phase will be stored at < -15°C until required. b) Montanide will be stored at +2 - +8°C until required. In Phase 1b, chemotherapy will be prepared and dispensed according to Pharmacy standard practice. Chemotherapy will include the following treatments: • cisplatin, IV (80 mg/m^2) and either; • 5-FU, 4000 mg/m^2 continuous infusion; • or capecitabine, 2000 mg/m^2/day, orally. In Phase 2 and Phase 2 Extension, chemotherapy will be prepared and dispensed according to Pharmacy standard practice. Chemotherapy will include the following treatments: • cisplatin, 80 mg/m^2, IV and either; • 5-FU, 4000 mg/m^2 continuous infusion; • or capecitabine, 2000 mg/m^2/day, orally. • Or oxaliplatin, 130 mg/m^2, IV and capecitabine, 2000 mg/m^2/day, orally.
Dose and Schedule	**Phase 1b** IMU-131 A total of 3 injections of IMU-131-Montanide emulsion (IMU-131) at a particular dose will be given to patients in the Phase 1b study (on Days 0, 14, and 35), with chemotherapy cycles every 21 days starting from Day 14.

	IMU-131 is formulated into either a low, medium or high dose with the concentration of each dose remaining constant while the injection volume varies: Low dose: 10 µg (peptide P467 antigen equivalent) P467-CRM197 in 50 µL PBS buffer and 50 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.1mL injection volume; Mid dose: 30 µg (peptide P467 antigen equivalent) P467-CRM197 in 150 µL PBS buffer and 150 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.3mL injection volume or; High dose: 50 µg (peptide P467 antigen equivalent) P467-CRM197 in 250 µL PBS buffer and 250 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.5mL injection volume. Patients will be enrolled in cohorts of up to 6 patients at 1 of 3 escalating dose levels of IMU-131: Cohort 1 - 10 µg as a 0.1 mL injection Cohort 2 - 30 µg as a 0.3 mL injection Cohort 3 - 50 µg as a 0.5 mL injection Chemotherapy Chemotherapy will include the following treatments, the dose and duration of which may be varied by the investigator as clinically indicated for the patient: Chemotherapy will be administered to all patients as a 21-day regimen starting 14 days (+ or – 1 day) after first IMU-131 vaccination: cisplatin, IV (80 mg/m^2 on Day 14, then every 21 days) and either 5-FU, 4000 mg/m^2 CIV (administered as 1000 mg/m^2/day as continuous infusion for 96 hours on days 14 to 17, then every 21 days) or capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 14 to 27, then every 21 days). Chemotherapy will be administered in 21-day cycles as tolerated or for any other reason to discontinue chemotherapy treatment as determined by the investigator for the clinical care of the patient. **Phase 2** IMU-131 Injections of IMU-131-Montanide emulsion (IMU-131) at 50µg will be given to patients in the 'IMU-131 plus chemotherapy' group in the Phase 2 study on Days 0, 14, 35, 77, 140 and then every 63 days. **Phase 2 Extension** IMU-131 A total of 3 injections of IMU-131-Montanide emulsion (IMU-131) at a

	particular dose will be given to patients in the Phase 2 dose escalation study on Days 0, 14, and 35, and then every 63 days with chemotherapy cycles every 21 days (to a maximum of 6 cycles) starting from Day 0. IMU-131 is formulated into a 100µg dose in a 1.0 mL injection volume by mixing 100 µg (peptide P467 antigen equivalent) P467-CRM197 in 500 µL PBS buffer with 500 µL Montanide ISA 51 sterile adjuvant resulting in a 1.0 mL injection volume. Cohort 1 – 100 µg Cohort 2 – 200 µg Refer to the study pharmacy manual for detailed IMU-131 vaccine preparation and administration instructions. <u>Chemotherapy in Phase 2 and Phase 2 Extension</u> Chemotherapy will include the following treatments, the dose and duration of which may be varied by the investigator as clinically indicated for the patient. Chemotherapy will be administered to all patients as a 21-day regimen starting at Day 0 and consisting of: cisplatin by intravenous administration at 80 mg/m^2 on the first day of each cycle and either 5-FU, 4000 mg/m^2 CIV (administered as 1000 mg/m^2/day as continuous infusion for 96 hours on days 1 to 4 of each cycle) or capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 1 to 14 of each cycle), or oxaliplatin, by intravenous administration at 130 mg/m^2 on Day 1 of each cycle and capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 1 to 14 of each cycle). Chemotherapy will be administered in 21-day cycles as tolerated to a maximum of 6 cycles. One or more chemotherapy treatments may be varied by dose, frequency or discontinued completely as determined by the investigator for the clinical care of the patient.
Phase 1b Study Procedures	**Physical Examination (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)** The physical examination will include an evaluation of body systems (e.g. cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). **Height, Weight and Vital Signs (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)** Body height (at screening visit only), weight, and vital signs (blood pressure, pulse and temperature) will be measured. **Radiographic Assessment (Screening, Days 56, 98, LTM visits)** For all patients, a radiographic assessment will be performed at Screening (for inclusion criteria assessment), and at Day 56, Day 98 and at long term maintenance visits until disease progression.

	Assessment of the tumor will include evaluation according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1). **Cardiac Assessment (Screening, Day 56)** Cardiac assessment of suitability for inclusion in the study and on Day 56 will be performed by the study investigator and be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation of left ventricular ejection fraction (LVEF) by echocardiography or MUGA scan. **Laboratory Assessments** Hematology and serum chemistry analyses will be performed by an accredited central laboratory. Immunological analysis will be performed by an accredited specialist immunology laboratory. **a) Safety Laboratory Assessments (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)** Blood samples of approximately 10 mL per visit for the assessment of hematological and serum chemistry parameters will be collected and processed in accordance with the central laboratory study manual. <u>Safety laboratory panels are defined as follows:</u> Human immunodeficiency virus (HIV 1/2 antibodies), hepatitis B (HBsAg reactive) and hepatitis C (HCV ribonucleic acid [RNA] qualitative) (at screening only). <u>Hematology:</u> Hematology to include CBC, including RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, C-reactive protein (CRP). <u>Serum Chemistry:</u> BUN or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT. **b) Immunologic Assessments (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)** Prior to each vaccination a 1 x 8 mL whole blood sample for humoral immunity will be obtained from the patient at Days 0, 14, 35, 56, 77, 98 and at LTM visits. Additionally, on Days 0, 56 and at each LTM visit, 5 x 8 mL heparinized blood samples will be collected for peripheral blood mononuclear cell (PBMC) isolation and analysis of cellular parameters. **HER2/neu overexpression (Screening)** Confirmation of HER2/neu overexpression is required for inclusion in this study. However, patients with IHC HER2 ++ expression without confirmation of overexpression by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic in situ hybridization [CISH]) may be included in Phase 1b with agreement

	of Imugene Limited. A previous pathology result confirming HER2/neu overexpression is acceptable. If analysis of a tumor biopsy is required for confirmation of HER2/neu overexpression then this may be achieved via analysis of a fresh or archived tissue sample. If a biopsy sample is used to determine HER2/neu overexpression then analysis of intra-tumor T cells for CD8+, CD4+, Th1, Th2, Tregs (Foxp3+ CD25+) will also be performed if these analyses are available at the pathology lab conducting HER2/neu overexpression analysis. HER2/neu analysis will be conducted at each centre's local pathology laboratory by immunohistochemistry (IHC) and fluorescent *in situ* hybridization [FISH], brightfield double *in situ* hybridization [BDISH] or chromogenic *in situ* hybridization [CISH] if IHC result is equivocal. Using the IHC method an unequivocal result of HER2 overexpression is defined as HER2 +++, an equivocal result is defined as HER2 ++, and a negative result is defined as HER2 +. If equivocal result (IHC HER2 ++) then additional analysis via FISH, BDISH or CISH will be conducted for confirmation of HER2 overexpression. The definition of FISH, BDISH or CISH positivity in gastric or gastro–esophageal junction cancer is a HER2: chromosome 17 ratio of ≥2.0. **ECOG performance grade (Screening)** The ECOG performance grade for screening evaluation should be determined using the criteria defined in Appendix 3: ECOG Performance Status Scale. **Vaccination site evaluation (Days 2, 16, 37)** The purpose of vaccination site evaluation is to determine the nature and frequency of local/vaccination site reactions. The vaccination site should be evaluated for local effects of the vaccine injection including pain, tenderness; erythema/redness and swelling/induration (see Section 9.7.1 Local (injection site) Adverse Event Intensity for further details). All local vaccination site effects are to be reported in the CRF and graded according to Table 4: Grading of Local Adverse Event Intensity presented in Section 9.7.1. Photographs will be taken during vaccination site evaluation if there are visible local injection site reactions. **Pregnancy Test (Screening, Days 0, 14, 35, 98, LTM visits)** For female patients of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of each vaccine dose. A negative pregnancy test result is required before the patient may receive the investigational product. If urine pregnancy test is positive then confirmation of pregnancy will be by BHCG blood test. If BHCG blood test is negative then vaccination schedule may resume.

Phase 2 and Phase 2 Extension Study Procedures	**Physical Examination (Screening, Baseline, Days 21, 42, 63, 84, 105, 126 then every 42 days and EoT visit)** The physical examination will include an evaluation of body systems (e.g. cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). After the Baseline physical examination, a symptom-directed physical examination is allowed at subsequent visits at the investigator's discretion. **Height, Weight, Vital Signs, Concomitant Medications, Concomitant Procedures and Adverse Events (at each study visit, excluding post-treatment follow-up visits)** Body height (at screening visit only), weight, and vital signs (blood pressure, pulse and temperature) will be measured and concomitant medications, concomitant procedures and adverse events will be documented. **Radiographic Assessment (Baseline, Days 42, 84, 126 then every 42 days)** For all patients, a radiographic assessment will be performed at Baseline (assessment allowed up to 14 days before Baseline Visit), Days 42, 84, 126 then every 42 days until disease progression. Assessment of the tumor will include evaluation according to RECIST 1.1. In the Phase 2 extension, a repeat scan may be performed as an unscheduled visit at the investigator's discretion to confirm progression 4-6 weeks after the date of the original scan indicating progression. If progression is confirmed the original date of progression will be used for disease assessment. **Cardiac Assessment (Screening, Day 84 then every 84 days and EoT visit)** Cardiac assessment to be performed at Screening, on Day 84 then every 84 days and at EoT visit. It will be performed by the study investigator and be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation of left ventricular ejection fraction (LVEF) by echocardiography or MUGA scan. **Laboratory Assessments** Hematology and serum chemistry analyses will be performed by an accredited local laboratory. Analysis of vaccine-specific cytokine levels, in-vitro inhibition of tumor cell growth, intra-tumor T cell and biomarker analysis will be performed by an accredited central laboratory. Humoral and cellular immunological analysis will be performed by an accredited specialist central immunology laboratory. Unused blood /serum and/or tissue samples collected during the study from patients who have signed an appropriate informed consent form may be stored and used for future research. The coded samples may be stored up to 15 years after the clinical study ends. A patient may contact the investigator to have their unused samples destroyed at any time during the

	storage period. Results from the future use studies will not be shared with patients. **1) Safety Laboratory Assessments (Screening, Baseline, Days 21, 42, 63, 84, 105, 126 then every 42 days and EoT visit)** Blood samples of approximately 10 mL per visit for the assessment of hematological and serum chemistry parameters will be collected and processed in accordance with local laboratory procedures and reference ranges. Safety laboratory panels are defined as follows: Human immunodeficiency virus (HIV 1/2 antibodies), hepatitis B (HBsAg reactive) and hepatitis C (HCV ribonucleic acid [RNA] qualitative) (at screening only). Hematology: Hematology to include CBC, including RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, C-reactive protein (CRP). Serum Chemistry: BUN or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT. **2) Exploratory Endpoint Laboratory Assessments (Baseline, Days 84 then every 84 days and EoT visit)** A 1 x 10 mL whole blood sample to assess vaccine-specific cytokine levels and in-vitro inhibition of tumor cell growth will be obtained from each patient at Days 0, 84 then every 84 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination. **3) Immunologic Assessments** **a) Humoral samples (Baseline, Days 21, 42, 63, 84, 126 then every 42 days and EoT visit)** A 1 x 10 mL whole blood sample for humoral immunity will be obtained from each patient at Days 0, 21, 42, 63, 84, 126 then every 42 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination. **b) Cellular samples (Screening [Phase 2 Extension only], Baseline, Days 84 then every 84 days and EoT visit)** Collection of 40 mL blood sample will be performed for PBMC isolation and analysis of cellular parameters at Days 0, 84 then every 84 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination. In Phase 2 Extension, an additional 40 mL blood sample will be performed for PBMC isolation and analysis of cellular parameters during

	screening visits after enrolment eligibility including HER2 over-expression is confirmed. **HER2/neu overexpression (Screening)** Confirmation of HER2/neu overexpression is required for inclusion in this study. A previous pathology result confirming HER2/neu overexpression is acceptable. If analysis of a tumor biopsy is required for confirmation of HER2/neu overexpression, then this may be achieved via analysis of a fresh or archived tissue sample. HER2/neu analysis will be conducted at each center's local pathology laboratory by immunohistochemistry (IHC) and fluorescent *in situ* hybridization [FISH], brightfield double *in situ* hybridization [BDISH] or chromogenic *in situ* hybridization [CISH] if IHC result is equivocal. Using the IHC method an unequivocal result of HER2 overexpression is defined as HER2 +++, an equivocal result is defined as HER2 ++, and a negative result is defined as HER2 +. If equivocal result (IHC HER2 ++) then additional analysis via FISH, BDISH or CISH will be conducted for confirmation of HER2 overexpression. The definition of FISH, BDISH or CISH positivity in gastric or gastro–esophageal junction cancer is a HER2: chromosome 17 ratio of ≥2.0. **ECOG performance grade (Screening, Baseline, Days 84 then every 84 days and EoT visit)** The ECOG performance grade should be determined using the criteria defined in Appendix 3: ECOG Performance Status Scale. **Pregnancy Test (at each study visit, excluding post-treatment follow-up visits)** For female patients of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of each vaccine dose. A negative pregnancy test result is required before the patient may receive the investigational product. If urine pregnancy test is positive, then confirmation of pregnancy will be by local laboratory BHCG blood test. If BHCG blood test is negative, then vaccination schedule may resume. **Intra-tumor analysis (Screening, Day 84 and post-progression)** A screening visit or archival tumor biopsy sample will be obtained for all patients for intra-tumor analysis (unless HER2 status has been confirmed previously and archival tissue is not available). An optional Day 84 and post-progression tumor biopsy sample will be requested from patients. These samples will be analyzed for intra-tumor T cells and biochemical markers. The screening visit biopsy sample may also be used to determine HER2/neu overexpression. **Unscheduled Visit** Unscheduled visits may be conducted at any time during Phase 2 by the

	investigator if clinically indicated for the care of the patient. An unscheduled visit may include any of the protocol required assessments listed in Section 8: Phase 2 Assessments. The exact assessments conducted at the unscheduled visit will be specified by the investigator and recorded in the CRF. Additional tests and procedures may be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor. **Phase 2 Only - Post-treatment Follow Up (FU) Visit (Every 42 days after EoT visit)** After disease progression, anti-cancer therapy and survival information will be collected every 6 weeks until death, withdrawal or end of trial. Anti-cancer therapy and survival information may be collected more frequently than every 6 weeks for quality control and data cleaning purposes. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 6 weeks until determination of progressive disease. All patients will be followed for radiographic change until determination of progressive disease and survival information and anti-cancer treatment until death, unless the patient requests to be withdrawn from radiographic change assessment and survival follow-up contact or the trial ends. Requests for withdrawal must be documented in the source documents and signed by the investigator. Phase 2 extension patients will no longer complete post-treatment follow up visits.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7 for Phase 1b and Section 8 for Phase 2 and Phase 2 Extension) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 1: Schedule of Activities Phase 1b

	Screen	**Dose 1 Period**		**Dose 2 Period** (+/- 3d)		**Dose 3 Period** (+/- 3d)		**End of Treatment Visit** (+/- 3d)	**Chemo only Visit** (+/- 7d)	**Start of long term maintenance**[h] (+/- 7d)	**Follow-up Post-Withdrawal Visit** (-2d, +16d)
Study Days	-21d to -1d	0	2	14	16	35	37	56	77	98	30 – 40 days after last vac
IMU-131 Vaccination		X		X		X				X[f]	
Chemotherapy[d]				X		X		X	X	X	
Informed Consent	X										
Demographics and prior medications	X										
Medical History	X										
Cancer History	X										
Physical Exam	X	X		X		X		X	X	X	X
Weight and vital signs (temp, BP, pulse)	X	X		X		X		X	X	X	X
Height	X										
Vaccination Site Evaluation/local effects			X		X		X				
ECOG performance status	X										
Radiographic Assessment[g]	X							X		X	

	Screen	**Dose 1 Period**		**Dose 2 Period** (+/- 3d)		**Dose 3 Period** (+/- 3d)		**End of Treatment Visit** (+/- 3d)	**Chemo only Visit** (+/- 7d)	**Start of long term maintenance**[h] (+/- 7d)	**Follow-up Post-Withdrawal Visit** (-2d, +16d)
Study Days	-21d to -1d	0	2	14	16	35	37	56	77	98	30 – 40 days after last vac
Cardiac Assessment[j]	X							X			
Tumor biopsy for HER2 analysis[k]	X										
Urine Pregnancy Test[a]	X	X		X		X				X	X
HIV, Hepatitis	X										
Hematology, Chemistry[b]	X	X	`	X		X		X	X	X	
Immunology[c]		X		X		X		X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (by interview with patient)[e]		X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Activities Long Term Maintenance

	Start of Long Term Maintenance[h] (LTM) (+/- 7d)	**LTM Visit 1** (+/- 14d)	**LTM Visit 2** (+/- 14d)	**LTM Continuing** (+/- 14d)	**Follow-up Post-Withdrawal Visit** (-2d, +16d)
Study Days	98	182	266	Every 84 days	30 – 40 days after last vac
IMU-131 Vaccination	X	X	X	X	
Chemotherapy[i] (If not ceased in Phase 1b)	X	Day 98 then every 21 days until chemotherapy is ceased[d]			
Physical Exam including weight and vital signs (temp, BP, pulse)	X	X	X	X	X
Radiographic Assessment[g]	X	X	X	X	
Urine Pregnancy Test[a]	X	X	X	X	X
Hematology, Chemistry[b]	X	X	X	X	
Immunology[c]	X	X	X	X	
Concomitant Treatments	X	X	X	X	X
Adverse Events (by interview with patient)[e]	X	X	X	X	X

Footnotes for Schedule of Activities – Phase 1b and Long Term Maintenance

[a] Negative urine pregnancy test required for women of childbearing potential at screening and prior to each vaccination. If positive urine test vaccination may be delayed until negative BHCG blood test.

[b] Hematology and serum chemistry to be performed at Screening, Days 0, 14, 35, 56, 77, 98 and at each LTM visit.

[c] 1 x 8 mL (i.e. 1 tube) whole blood sample for humoral immunity on days 0, 14, 35, 56, 77, 98, and each LTM visit and 5 x 8 mL heparinized blood on days 0, 56 and each LTM visit for cellular immunity. To be taken prior to vaccination at vaccination visits, including during long term maintenance.

[d] Chemotherapy for all patients: cisplatin, IV (80 mg/m^2 on Day 14, then every 21 days) and either 5-FU, 4000 mg/m^2 CIV (administered as 1000 mg/m^2/day as continuous infusion for 96 hours on Days 14 to 17, then every 21 days) or capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on Days 14 to 27, then every 21 days). Body weight to be measured and body surface area to be calculated based on weight and baseline height at the start of each 21 day chemotherapy cycle. Chemotherapy continues until ceased by the investigator as clinically indicated for the care of the patient. To document compliance while away from the clinic, patients will record capecitabine treatment in a patient diary.

[e] Photographs will be taken for vaccination site evaluation if there are visible local injection site reactions.

[f] First booster dose of IMU-131 for long-term maintenance. Booster doses continue every 12 weeks.

[g] Radiographic assessment to occur within the screening period, then at Days 56, 98 and each LTM visit. Radiographic assessment continues until disease progression according to RECIST 1.1 response criteria or if unacceptable toxicity occurs.

[h] Patients who complete Day 56 will continue in long term maintenance. Treatment and procedures for long term maintenance are according to Table 2: Schedule of Activities Long Term Maintenance.

[i] If not ceased prior to start of long term maintenance then chemotherapy continues until ceased by the investigator as clinically indicated for the care of the patient.

[j] Cardiac assessment includes 12-lead ECG and evaluation of LVEF by echocardiography or MUGA scan.

[k] No tumor biopsy is required if a previous pathology result or archival tissue is available confirming HER2/neu expression consistent with Inclusion Criteria #6.

Table 3: Schedule of Activities Phase 2 and Phase 2 Extension

	Screen	**Baseline**	**Week 2[K]** (+/- 3d)	**Week 3** (+/- 3d)	**Week 5[K]** (+/- 3d)	**Week 6** (+/- 3d)	**Week 9** (+/- 7d)	**Week 11[K]** (+/- 7d)	**Week 12** (+/- 7d)	**Week 15** (+/- 7d)	**Week 18** (+/- 7d)	**Week 20[K]** (+/- 7d)	**EoT Visit[O]** (+/- 7d)	**Post- treatment FU Visit[Q,R]** (+/- 7d)
Study Days	-21d to -1d	0	14	21	35	42	63	77	84 repeat every 84 days (+/- 7d)	105	126 repeat every 84 days (+/- 7d)	140 repeat every 63 days (+/- 7d)	At least 28 (+/- 7) Days after last dose	Every 42 days after EoT
Survival/anti-cancer treatment														X
IMU-131 Vaccination		X	X		X			X				X		
Chemotherapy[D,F]		X		X		X	X		X	X				
Informed Consent	X													
Demographics and prior medications	X													
Medical History	X													
Cancer History	X													
Physical Exam[N]	X	X		X		X	X		X	X	X		X	
Weight and vital signs (temp, BP, pulse)[L]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X													
ECOG performance status	X	X							X				X	
Radiographic Assessment[E]		X				X			X		X			X[G]
Cardiac Assessment[H]	X								X				X	

	Screen	**Baseline**	**Week 2[K]** (+/- 3d)	**Week 3** (+/- 3d)	**Week 5[K]** (+/- 3d)	**Week 6** (+/- 3d)	**Week 9** (+/- 7d)	**Week 11[K]** (+/- 7d)	**Week 12** (+/- 7d)	**Week 15** (+/- 7d)	**Week 18** (+/- 7d)	**Week 20[K]** (+/- 7d)	**EoT Visit[O]** (+/- 7d)	**Post- treatment FU Visit[Q,R]** (+/- 7d)
Study Days	-21d to -1d	0	14	21	35	42	63	77	84 repeat every 84 days (+/- 7d)	105	126 repeat every 84 days (+/- 7d)	140 repeat every 63 days (+/- 7d)	At least 28 (+/- 7) Days after last dose	Every 42 days after EoT
Tumor biopsy[I]	X								X[J]				X[J]	
Urine Pregnancy Test[A]	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, Hepatitis[M]	X													
Hematology, Chemistry[M]	X	X		X		X	X		X	X	X		X	
Exploratory endpoint labs[B]		X							X				X	
Immunology – humoral[C]		X		X		X	X		X		X		X	
Immunology - cellular[C]	X[P]	X							X				X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes for Schedule of Activities – Phase 2 and Phase 2 Extension

A Negative urine pregnancy test required for women of childbearing potential at screening and prior to each vaccination. If positive urine test vaccination may be delayed until negative BHCG blood test.

B A 1 x 10 mL whole blood sample to assess vaccine-specific cytokine levels and in-vitro inhibition of tumor cell growth will be obtained from each patient at Days 0, 84 then every 84 days and at EoT visit.

C 1 x 10 mL (i.e. 1 tube) whole blood sample for humoral immunity at Baseline, Days 21, 42, 63, 84, 126 then every 42 days and EoT visit and 40 mL blood sample at Screening (Phase 2 Extension only), Baseline, Days 84 then every 84 days and EoT visit for cellular immunity. To be taken prior to vaccination at Baseline visit.

D Chemotherapy will be administered as a concomitant therapy to all patients as a 21-day regimen consisting of: cisplatin by intravenous administration at 80 mg/m2 on the first day of each cycle and either 5-FU, 4000 mg/m2 CIV (administered as 1000 mg/m2/day as continuous infusion for 96 hours on days 1 to 4 of each cycle) or capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle), or capecitabine for 14 days at 2000 mg/m2/day, orally (administered as 1000 mg/m2 twice daily morning and evening for a total of 2000 mg/m2/day on days 1 to 14 of each cycle) and oxaliplatin, by intravenous administration at 130 mg/m2 on Day 1 of each cycle. Body weight to be measured and body surface area to be calculated based on weight and baseline height at the start of each 21-day chemotherapy cycle. Chemotherapy continues until ceased by the investigator as clinically indicated for the care of the patient. To document compliance while away from the clinic, patients will record capecitabine treatment in a patient diary.

E Radiographic assessment to occur within 14 days prior to Baseline Visit, then at Days 42, 84, 126 every 42 days thereafter. Radiographic assessment continues until disease progression according to RECIST 1.1 response criteria, withdrawal or end of trial.

F Chemotherapy continues for up to 6 cycles until disease progression or until ceased by the investigator as clinically indicated for the care of the patient, whichever occurs first.

G Radiographic assessment according to RECIST 1.1 response criteria at post-treatment follow-up visit only for patients who have ended study treatment prior to disease progression.

H Cardiac assessment will be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation LVEF by echocardiography or MUGA scan at Screening, Days 84 then every 84 days and at EoT visit.

I No tumor biopsy is required if a previous pathology result or archival tissue is available confirming HER2/neu expression consistent with Inclusion Criteria #6.

J Optional Day 84 and post-progression tumor biopsy (which may be provided at any time post progression).

K Visit only for 'IMU-131 plus chemotherapy' group.

L Record temperature 30min (+/- 10mins) after each IMU-131 vaccination.

M Local laboratory testing. Safety lab samples can be drawn up to 72 hours before any on-study clinic visit.

N A targeted, symptom directed physical examination may be performed at visits occurring after the Baseline Visit.

O When progressive disease or withdrawal from study has been confirmed, EoT visit will be conducted at least 28 Days (+/- 7) after last dose of study medication. AEs to be checked at least 28 days after last study treatment per Section 9.2: Reporting Period.

P Phase 2 Extension only: Screening 40 mL cellular immunity blood sample after enrolment eligibility including HER2 over-expression is confirmed.

Q Phase 2 only: Phase 2 Extension patients will no longer complete Post Treatment Follow Up Visits

R R End of trial is defined as 28 days post the last patient completing the end of treatment visit.

1. INTRODUCTION

1.1. Indication

IMU-131 is a single peptide composed of 3 individual B-cell epitope peptide sequences selected from the HER2/neu structure which induces the patient's own B-cells to produce endogenous anti-HER2/neu antibodies. IMU-131 is being developed for the treatment of patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or gastroesophageal junction (referred to as advanced cancer of the stomach or ACS).

1.2. Background and Rationale

Almost one million new cases of gastric cancer were estimated to have occurred in 2016, making it the fifth most common malignancy in the world, and gastric cancer is the third leading cause of cancer death worldwide (Siegel et al., 2016), and is the second most common cause in many Asian countries, such as China, Japan, and Korea.

Gastric cancer is considered an unmet medical need. Advanced cancer of the stomach (ACS) differs in its global epidemiology and patient predisposition. Whereas the incidence of ACS is lower in countries of the Western world, it is prevalent in countries of the Eastern hemisphere. Asia covers a large geographical area: it has more than 40 countries and diverse ethnic groups. Socioeconomic conditions, political status, and health-care systems vary widely between different Asian countries. Data for individual countries show that gastric cancer is the most common cancer in Japan and the second most common in China and Korea; in Singapore, Taiwan, and Philippines, gastric cancer is one of the five most common types of cancer. Its prevalence is high in countries with limited financial resources and in socially underprivileged individuals. This situation leads to the problem of delivery of optimal treatment options, particularly in countries with limited financial resources and particularly to socially underprivileged individuals.

ACS occurs predominantly in a primarily inoperable state with metastatic spread to distant lymph nodes or to inner organs and – if operable – tends to recur frequently. The American Cancer Society reports that patients with Stage IIIc and IV gastric cancer can expect 5-year survival rates of only 9% and 4%, respectively (American Cancer Society, 2014). For initial systemic treatment for metastatic and locally advanced cancer where local treatment is not indicated, 2-drug combinations are preferred over 3-drug combinations due to its lower toxicity − generally a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], intravenous [IV] or capecitabine, oral) and platinum-based (e.g., cisplatin, IV or oxaliplatin, IV) chemotherapy − are recommended in the current US National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology - Gastric Cancer (NCCN, 2017; NCCN 2018).

The transmembrane tyrosine kinase receptor HER2/neu (Human Epidermal Growth Factor Receptor 2) is also known as Neu, Erb-2, CD340, or p185 but is most commonly referred to as HER2/neu (Coussens et al, 1985). It is a member of the epidermal growth factor receptor (EGFR/ErbB) family. Amplification or overexpression of this receptor has been shown to play an important role in pathogenesis and progression of aggressive subsets of several types of cancer including ACS, breast cancer, ovarian cancer, uterine cancer (Santin et al, 2008; Tan and Yu, 2007), endometrial cancer, and others. It has been found to be

overexpressed in 15% to 25% of patients with gastric cancer (Hofmann et al, 2008; Park et al, 2006; Yano et al, 2006; Zhang et al, 2009) where it is associated with a worse prognosis, more aggressive disease, and poorer survival. In tumors where HER2/neu is overexpressed, signaling through this receptor proceeds through the MAPKinase - PI3K/Akt - Phospholipase C - Protein Kinase C - STAT cascade promoting cell proliferation and opposing apoptosis (Roy and Perez, 2009). Where it is overexpressed, HER2/neu is typically the primary driver of proliferation for the malignant cells.

The Phase 3 Trastuzumab for Gastric Cancer (ToGA) trial compared 5-FU (or capecitabine) + cisplatin ± trastuzumab in 594 patients with HER2/neu overexpressing gastric or GEJ adenocarcinoma. Median overall survival (OS) was significantly improved with trastuzumab compared to chemotherapy alone: 13.5 vs 11.1 months (p=0.0048). The overall response rates were 47.3% in the trastuzumab + chemotherapy arm vs 34.5% in the chemotherapy alone arm (p=0.0017). Based on these data, the combination of trastuzumab plus 5-FU and cisplatin chemotherapy has become registered as the standard therapeutic option in combination with chemotherapy in first line setting in some countries. Trastuzumab is costly, however, and has been associated with a serious decline in heart function for some patients. Other potentially serious side effects include infusion reactions, pulmonary edema, and respiratory distress. A pharmacoeconomic analysis of trastuzumab in gastric cancer conducted by NICE in 2010 concluded that it was not cost effective (NICE, 2010) and a pharmacoeconomic analysis of the ToGA data concluded that trastuzumab treatment may only be cost effective for a subgroup of gastric cancer patients defined post hoc who were immunohistochemistry (IHC) 3+ for HER2/neu at baseline. Using trastuzumab to treat all HER2-positive populations is not likely to be cost effective (Shiroiwa et al, 2011).

Since trastuzumab may not be available or affordable in certain parts of the world including even parts of Western Europe and might be associated with adverse effects for certain patients, there is a need for alternative treatment options. One alternative approach to HER2/neu inhibition may be the induction of endogenous anti-HER2/neu antibodies by a patient's own B-cells after treatment with a HER2/neu-directed vaccine, such as IMU-131. Active specific immunization against HER2/neu amino acid sequences may result in persisting antibody formation in humans. This approach in a predecessor formulation to IMU-131 (PEV6C) was highly effective in reducing tumor growth in animal models of HER2/neu overexpressing tumors and has undergone Phase 1a testing that demonstrated the safety and immunogenicity of the vaccine (Wiedermann et al, 2010).

This study has a 2-part design. The Part 1 (Phase1b) component is aimed at determining the safety of IMU-131 and an optimal immunological dose of IMU-131, to carry into the Part 2 (Phase 2) dose expansion component of the study. Part 2 will immediately follow Part 1 and is designed to evaluate efficacy and to further characterize the safety and clinical activity of IMU-131 in combination with chemotherapy in HER2/neu overexpressing advanced gastric or GEJ adenocarcinoma.

1.3. IMU-131 (HER2/neu Peptide Vaccine)

The investigational medicinal product IMU-131 is a sterile solution in PBS buffer of the Her-2/neu antigen P467 linked to non-toxic diphtheria CRM197 protein (P467-CRM197) [redacted]. The peptide antigen component

of IMU-131 is a single peptide design composed of 3 individual B-cell epitope peptide sequences selected from the HER2/neu structure and are the identical peptides being investigated in the predecessor formulation PEV6C (Wiedermann et al, 2010). Polyclonal antibodies generated against IMU-131 peptides bind three separate regions of the HER2 receptor in domains III and IV thereby inhibiting intracellular signaling and inducing antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). HER2/neu, gene product of erbB2/neu protooncogene, is a 185 kDa protein that belongs to the epidermal growth factor receptor family. It consists of a cysteine rich extracellular domain (ECD) with several glycosylation sites, a hydrophobic transmembrane domain, and an intracellular conserved tyrosine kinase domain. HER2/neu is weakly detectable in epithelial cells of normal tissues but is overexpressed in 15 - 25% of several cancers including primary breast, gastric and prostate cancer, and has been linked with a poor prognosis, more aggressive disease progression and high risk of cancer relapse. The overexpression seems to be stable and homogenous in primary tumors as well as their metastases. These findings suggest HER-2/neu may be an attractive target of cancer immunotherapy. In vitro and in vivo animal experiments with an earlier formulation of IMU-131, PEV6C, have corroborated this approach and have shown the ability to generate an effective antibody response by human B-cells (Wagner et al, 2007).† These antibodies were able to induce ADCC and CDC and to inhibit the proliferation of HER2/neu overexpressing tumor cells in vitro. PEV6C was also able to effectively inhibit the emergence of HER2/neu overexpressing breast tumors in a transgenic mouse model (Roy and Perez, 2009).

IMU-131 is a HER2/neu antigen peptide – adjuvant emulsion (P467-CRM197 – Montanide emulsion) which is injected intramuscularly (IM) into the patient to stimulate innate immunity in response and is processed by antigen presenting cells. The immune system then generates specific adaptive immunity to the HER2/neu antigen peptides. This ultimately leads to the development of B-cells that secrete endogenous HER2/neu-specific antibodies that block binding HER2 signaling. Blocking HER2 signaling inhibits proliferation and enables apoptosis in HER2/neu overexpressing tumor cells. Antibody binding to these cells can also signal for additional immunologic clearance through ADCC and CDC. Immunization with this multi-epitope vaccine performed in a c-neu transgenic mouse model demonstrated that the vaccine led to delayed onset of tumor growth and reduced tumor progression in vivo (Wagner et al, 2007), providing the rationale to move into human clinical testing.

Several strategies of combining cancer vaccines with chemotherapy have been tested. Various chemotherapy regimen have been evaluated in combination with immunotherapies, e.g. vaccines, with regards to the beneficial effect chemotherapy might have in enhancing the immune response triggered by vaccines. These studies have revealed that immune-stimulatory cancer vaccines can be safely used in combination with immunosuppressive chemotherapies to condition the immune system and to create an environment where cancer vaccines have a better chance of success. Among the chemotherapies tested to enhance immune responses from vaccines, the underlying mechanism of supporting the immune response of vaccines are favorably described for 5-FU- and Cisplatin-based regimen and provide a rationale for the combination of both chemotherapies with an immune-stimulatory vaccine (Weir et al, 2011). A study of the effect of 5-FU chemotherapy on patients diagnosed with lung cancer reported that immunization with an anti-idiotype antibody, designated CeaVac (a monoclonal antibody with an internal image of CEA), had

no qualitative or quantitative effect on the anti-CEA immune response (Foon et al, 1999). Gastric cancer patients have been successfully immunized with G17DT immunogen

resulting in anti-gastrin titers while receiving simultaneous cisplatin and 5-FU chemotherapy (Alanji et al, 2006). Matsushita et al (2013) in a Phase 1 trial treated patients with advanced gastric cancer using a vaccine containing a mixture of synthetic peptides and oral tegafur/uracil leucovorin. Among the 10 treated patients the responses were 1 Partial Response and 7 Stable Disease.

In the phase 1 study of IMU-131 predecessor, PEV6C, eight of the 10 patients exhibited an increase in HER2/neu-specific antibody titers directed against vaccine peptides as well as native HER2/neu protein. A marked increase in cellular immune responses was observed in the majority of vaccinated patients. In addition, the number of CD4+CD25+Foxp3+ T-regulatory cells was markedly reduced following vaccination, suggesting the vaccine was effective in overcoming immunological tolerance to HER2/neu. These data support that the 3 peptide sequences contained in IMU-131 are effective in generating antibodies against HER2/neu as well as inducing additional immunologic changes that increase the activity of cellular immunity and reduce immunologic tolerance to HER2/neu expressing cells.

The Phase 1b study has been designed with 2 immunizations prior to initiating chemotherapy so that there is a maximum chance that vaccine-specific B and T cells can be primed, antibody production initiated, and memory cells induced. This will provide the optimal environment for patients to generate high anti-HER2 antibody titres and for the appropriate recommended phase 2 dose to be accurately determined.

A common side effect of chemotherapy, including cisplatin and 5-FU treatment of advanced or metastatic gastric cancer is myelosuppression (Florea and Büsselberg, 2011; Kim et al, 1993; Kim et al, 2000; Kim, 2005; Leong, 2005; Ozkan et al, 2005) which may lead to a reduction in available B cell lymphocytes and the potential antibody response to IMU-131. Moreover, memory B cells within the lymph nodes and induced plasma cells will be less affected than if vaccination is started post chemotherapy because patients undergoing chemotherapy do not lose their vaccine memory to vaccines like diphtheria or tetanus when these vaccinations occur before the start of chemotherapy (Haining et al, 2005; Laws et al, 2005). From vaccinology point of view it is therefore highly recommended to vaccinate before onset of chemotherapy (Giese, 2016; Wiedermann et al, 2016).

Generating high antibody titers are critical when using vaccines to induce antibodies to immuno-oncology targets. For example, the anti-EGF B-cell vaccine 'CIMAvax' for non-small cell lung cancer (NSCLC) demonstrates that patients' survival rate increases with amount of antibody production with a strong correlation between survival rates and level of antibody titres with Poor Antibody Responders (PAG; maximal antibody titer < 1:4000) surviving a mean of 5.5 months vs Good Antibody Responders (GAR; maximal antibody titer > 1:4000) surviving a mean of 10.5 months and super Good Antibody Responders (sGAR, maximal antibody titer >1:64000) surviving a mean of 25.6 months (Gonzalez et al, 2003; Rodriguez et al, 2010; Neninger et al, 2009).

A study of the anti-EGF B-cell vaccine 'CIMAvax' for NSCLC demonstrated stronger antibody production and longer survival rates in patients when CIMAvax was initiated prior to first–line chemotherapy (Neninger et al, 2009). The results of this study show antibody

titers were significantly higher compared to when chemotherapy preceded vaccination. In this study the geometric mean of maximal antibody titers was 1:76,109, compared to 1:3160 when chemotherapy preceded vaccination with 95% of the patients classified as Good

Antibody Responders (GAR, maximal antibody titer > 1:4000) compared to 51% reaching this threshold when chemotherapy preceded vaccination. Moreover 55% patients vaccinated prior to chemotherapy were classified as super Good Antibody Responders (sGAR, maximal antibody titer > 1:64000) whereas only 2.8% of patients were classified as sGAR when vaccinated after chemotherapy. Furthermore, it is important to note that the increase in immunogenicity produced with pre-chemotherapy vaccinations of CIMAvax was associated with an increase in overall survival but was not associated with increased toxicity (Neninger et al, 2009).

Within the Phase 1b study as of the data cut-off of 07 November 2018, IMU-131 has been administered to 14 patients with advanced gastric or GEJ cancer at dose of 10 to 50 µg peptide P467 antigen equivalent (3 doses on Days 0, 14, and 35) with 11 completing the study through Day 56. No dose-limiting toxicities were reported for any patients. No injection site reactions were reported at 2 days post-dose for any patients; however, Grade 1 AEs of redness and itch on right upper arm in the same subject with onset 3 days after third injection of 50 µg dose and resolution without intervention the next day were assessed by the Investigator as possibly related to IMU-131. The Investigators assessed only 2 AEs as related to IMU-131 (Grade 2 hypoalbuminemia and Grade 3 hyponatremia in the same subject) and 4 AEs as possibly related to IMU-131 (Grade 2 weight loss and Grade 1 anorexia in the same subject, Grade 1 redness and itch in the same subject). No serious adverse reactions have been reported. Decreases in LVEF, which were substantial in 3 (27%) patients, were transient and had no clinical correlation.

In the Phase 1b study IMU-131 elicited anti-P467 and anti-HER-2 antibodies that increased both with increased doses and after subsequent doses. Of the 10 patients who have completed the study through Day 56 and had measurable disease at Baseline, 5 had a partial response, and 3 others had a measurable decrease in tumor size.

The preliminary immunology and clinical response data from Phase 1b are promising. Safety data to date indicate that IMU-131 is well tolerated with no significant local or systemic reactions, and no need for pretreatment or for modification to the dose or treatment schedule due to safety. The safety and immunological data from Phase 1b supported a dose of 50 µg peptide P467 antigen equivalent conjugated to CRM197 in a Montanide emulsion (IMU-131) as a 0.5 mL injection on Days, 0, 14, 35 followed by a booster 42 days later and subsequent boosters every 63 days (Wiedermann et. al., 2021).

The Phase 2 study has been designed with the treatment group (IMU-131 plus chemotherapy) receiving immunization and chemotherapy starting on the same day because 1) analysis of immunological responses in patients in Phase 1b did not show a detrimental effect of chemotherapy on the development of either anti-P467 or anti-HER-2 antibodies at any timepoint associated with chemotherapy treatment and 2) having the same chemotherapy schedule in the treatment and control groups in Phase 2 strengthens the statistical validity of the time-based secondary efficacy endpoint analysis.

The rationale to increase the dose of IMU-131 is justified by existing clinical data with no dose limiting toxicity during the Phase 1b study and selection of 50µg as recommended

phase 2 dose based on Her2/neu antibody development and response compared to the lower dose levels studied. In addition, safety data from the ongoing Phase 2 study supports dose escalation above 50µg IMU-131 because no IMU-131 related safety signals, dose limiting toxicities, or SUSARs have been detected. The Phase 2 dose escalation study will therefore explore whether an increased dose will produce earlier and stronger development of Her2/neu antibodies, which may potentially support the use of IMU-131 in patients who progress after developing resistance to trastuzumab (Rexer and Arteaga, 2012). The Phase 2 extension study will evaluate two dose levels for safety, efficacy, and immunogenicity. The safe administration of IMU-131 at higher doses will set the stage for a further Phase 2 extension study in second-line treatment of metastatic/advanced gastric and GEJ cancer in patients that have progressed under trastuzumab. Additional support for introducing higher doses of IMU-131 comes from two patients participating in the ongoing Phase 2 study. Two patients (SB03-202, SB03-204) erroneously received an initial 3 and 2 consecutive doses of 100ug IMU-131, respectively. These patients showed stronger and earlier Her2/neu antibodies relative to patients receiving the 50µg dose with an associated progression free survival of 42 and 36 weeks, respectively, with no significant adverse events indicating that patients may benefit from the higher doses of IMU-131.

It is hypothesized that administration of IMU-131 in combination with chemotherapy will prolong survival and may delay tumor progression and/or reduce tumor burden in patients with HER2/neu overexpressing gastric or GEJ adenocarcinoma. It is anticipated that due to the selective targeting of multiple epitopes on the HER2 receptor (including the epitope targeted by trastuzumab and the functionally important HER2 dimerization region) and the expected immune response, that IMU-131 could convey an efficacy advantage over trastuzumab as well as a potential safety, and/or a more favorable side effect profile, particularly over a longer period of dosing, due to the stimulation of the patient's own immune system. Lastly, IMU-131 may have a cost advantage over semi-synthetic antibodies, which may confer cost and therefore access advantages over trastuzumab.

[†]The original formulation of IMU-131 (or PEV6C) was composed of the three individual B-cell epitope peptides whereas the new, current formulation combines all three in a specific order resulting in a single fusion peptide of 49 amino acids in length. This new formulation of IMU-131 has shown improved stability as well as equal and improved immunogenicity compared to the original formulation.

1.4. Risk/Benefit analysis for IMU-131 (HER2/neu Peptide Vaccine)

It is anticipated that the information gained from this study will contribute to the development of a safe and effective anti-HER2/neu peptide vaccine. It is unknown whether patients will benefit from participation in this study. The investigational product-related risks to patients in this study are associated with the general risk of vaccination, however IMU-131 in the Phase 1b study revealed no systemic toxicities with only mild local injection site reactions. The volume of blood drawn over the study period is not expected to compromise patients.

The general risks to patients will arise from their common chemotherapy. Serious and potentially fatal specific and general risks are associated with cisplatin and either 5-FU or capecitabine combination chemotherapy, or oxaliplatin and capecitabine combination chemotherapy, that will be administered to patients on this trial. These treatments are standard care for this disease (NCCN, 2018) and are given in a standard fashion that is

familiar to all investigators, but all patients are likely to experience some chemotherapy-associated adverse events (AEs).

Vaccination-specific potential risks include the following:

Local reactions: An inflammatory reaction as manifested by redness, swelling, and/or tenderness may occur at the site of vaccine injection. Local reactions are expected to resolve within days to weeks without medical intervention and sequelae.

Systemic reactions: May include flu-like symptoms with low-grade fever, chills, and malaise. Experience to date with other peptide vaccines suggests that if such reactions occur, they resolve in days to weeks without therapy or limitation of daily activity. Serum sickness reactions due to deposition of antigen-antibody complexes or idiosyncratic immune responses not dependent on immune complexes could develop, resulting in damage to organs such as the liver or kidney. Such immune-mediated reactions have not been reported to date for HER2/neu peptide vaccines. Temporary ascending paralysis, the Guillain-Barré syndrome, may occur with any vaccine, although it is very rare.

Allergic reactions and anaphylaxis: Allergic and anaphylactic reactions are also possible. No such reactions have been observed to date.

The design of the Phase 1b study enables close medical monitoring of patients. Physical monitoring of patients occurs after each vaccination and 2 days post vaccination during each dose period. Cohort Review Committee (CRC) meetings and site teleconferences between the medical monitor and investigational site staff will occur regularly during the study.

Similarly, the design of the Phase 2 and Phase 2 Extension studies support appropriate medical monitoring of patients. Physical monitoring of patients occurs after each vaccination and at regular intervals during each study. Independent Data Monitoring Committee (IDMC) meetings during Phase 2 and CRC meetings during Phase 2 dose escalation, as well as site teleconferences between the medical monitor, Sponsor representatives and investigational site staff will occur regularly during the study.

Complete information for IMU-131 may be found in the Single Reference Safety Document, which for this study is the Investigator Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This phase1b/2 protocol is made up of 2 components.

Phase 1b aims to determine the safety and tolerability of IMU-131 and identify the Recommended Phase 2 Dose (RP2D) of IMU-131 in combination with chemotherapy in HER2/neu overexpressing ACS to carry into the Phase 2 dose expansion study. The Phase 2 component will be submitted as an amendment and will be initiated following completion of Phase 1b. Phase 2 will be designed to further characterize the safety and to explore clinical activity of IMU-131 in combination with chemotherapy in HER2/neu overexpressing ACS.

Phase 2 is an open-label, randomized, multicenter study designed to assess the clinical activity, immunogenicity, safety and tolerability of IMU-131. The length of Phase 2 will be approximately 30 months: 22 months' recruitment and an estimated 8 months' follow-up from completion of recruitment to realization of the required number of deaths. It is anticipated that an additional 3 months will be required to complete the analyses following realization of the last required death.

Phase 2 Extension

Dose escalation during Phase 2 is an open-label, multicenter, single arm dose escalation study with the same inclusion/exclusion criteria as Phase 2 and the same schedule of assessments as Phase 2 IMU-131+chemotherapy arm. The safety of each dose will be assessed by CRC after at least 3 patients have 3 doses of IMU-131 and one cycle of chemotherapy and have completed the 35 day DLT window. Two dose cohorts, consisting of 100μg and 200μg dose levels of IMU-131, will further characterize the safety, immunogenicity, and clinical activity of IMU-131 in combination with chemotherapy.

Phase 1b objectives:

- To evaluate the safety and tolerability of IMU-131 administered intramuscularly (IM) and initiated 14 days (+/- 1 day) prior to cisplatin, intravenous (IV) and either 5-FU, IV or capecitabine, oral chemotherapy in patients with HER2/neu overexpressing ACS;
- To identify the Recommended Phase 2 Dose of IMU-131, administered IM and initiated 14 days (+/- 1 day) prior to chemotherapy in patients with HER2/neu overexpressing ACS for evaluation in Phase 2.

Phase 1b exploratory objectives:

- Humoral and tumoral immunogenicity data will be used to further explore the mechanism of action for anti-tumor effects of IMU-131;
- Radiographic data will be used for an exploratory determination of Response Rate.

Phase 2 primary objective:

- To evaluate the clinical efficacy of IMU-131 plus chemotherapy compared to chemotherapy alone based on overall survival (OS).

Phase 2 secondary objectives:

- To evaluate other efficacy measures of IMU-131 plus chemotherapy compared to chemotherapy alone including progression-free survival (PFS), time to progression (TTP), disease control rate (DCR), objective response rate (ORR), duration of objective response (DOR) and change in tumor size (CTS) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) for the progression evaluation of radiographic data.
- To evaluate the safety profile of IMU-131 plus chemotherapy compared to chemotherapy alone.

Phase 2 exploratory objectives:

- To evaluate humoral and cellular immunogenicity data of IMU-131 plus chemotherapy compared to chemotherapy alone including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells.
- To evaluate the arm-specific associations between clinical outcome, intra-tumor T cells, regulatory and effector T and B cells, and serum and biochemical markers of tumor progression
- To evaluate arm-specific associations between clinical outcome and HER2 and PD- L1 expression in tumor tissue.
- To evaluate inhibition of in-vitro tumor cell growth and intra-cellular signaling processes by Her-2-specific antibodies (IgG).

Phase 2 Dose Escalation Primary Objective:

- To evaluate the safety and tolerability of 100µg and 200µg of IMU-131 in combination with chemotherapy.

Phase 2 Dose Escalation Secondary Objectives:

- To evaluate efficacy of IMU-131 plus chemotherapy including OS, PFS, TTP, ORR, DOR, DCR, and CTS according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) for the progression evaluation of radiographic data.

Phase 2 Dose Escalation Exploratory Objectives:

- To evaluate humoral and cellular immunogenicity data of IMU-131 plus chemotherapy compared to chemotherapy alone including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells.
- To evaluate the associations between clinical outcome, intra-tumor T cells, regulatory and effector T and B cells, and serum and biochemical markers of tumor progression.
- To evaluate associations between clinical outcome and HER2 and PD- L1 expression in tumor tissue.
- To evaluate inhibition of in-vitro tumor cell growth and intra-cellular signaling processes by Her-2-specific antibodies (IgG).

2.2. Endpoints

In Phase 1b, toxicity data for each cohort will be reviewed prior to each dose escalation by a Cohort Review Committee (CRC). The CRC consists of both Investigator site and Sponsor representatives. Investigator site representatives will include the Principal Investigator and any ancillary staff identified by the Principal Investigator. The Sponsor representatives will include the medical monitor and clinical trial manager and other designee. Each CRC meeting will be held after each dose cohort is complete and prior to initiation of the next dose cohort. The CRC will review the complete, pre-defined safety

and immunogenicity dataset from each dose cohort and will determine, with advice from the Principal Oncologist and Clinical Immunologist, the appropriate dose limiting toxicity (DLT) rule (see Sections 10.1.1 and 10.1.2 for details) and whether the study will proceed

to the next dose cohort. All patients in a dose cohort must have completed chemotherapy cycle 1 (35 days of the study, including 3 doses of IMU-131) prior to the CRC meeting and opening of the next higher dose cohort for enrollment.

Phase 1b endpoints:

- The safety and tolerability of IMU-131 will be evaluated by adverse events (AEs) and laboratory measurements. AEs and laboratory abnormalities will be graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.03;
- The recommended phase 2 dose will be evaluated by safety/tolerability and immunogenicity data for IMU-131 (P467-specific antibodies (IgG) and Her-2-specific antibodies (IgG) titers).

Phase 1b exploratory endpoints:

- Humoral and cellular immunogenicity data will include P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) in serum samples and vaccine-specific cytokine levels as well as analysis of regulatory and effector T and B cells taken across study visits. As prediction markers of tumor progression initial evaluation (prior first vaccination) of intra-tumor T cells and regulatory cells in tumor biopsies will be performed, when these tests are available at the hospital pathology laboratory.
- Radiographic data will be analyzed descriptively to explore Response Rate and provide information for sample size calculation for the Phase 2 study.

Phase 2 primary efficacy endpoint:

- OS measured from randomization to death due to any cause.

Phase 2 secondary efficacy endpoints:

- PFS measured from randomization to date of earliest progressive disease (PD) based on blinded central review according to RECIST 1.1 criteria, or to date of death from any cause.
- TTP measured from randomization to date of earliest PD based on blinded central review according to RECIST 1.1 criteria.
- DCR measured from randomization as the proportion of patients achieving a confirmed best overall response of complete response (CR), partial response (PR) or stable disease (SD) based on blinded central review according to RECIST 1.1 criteria.
- ORR measured from randomization as the proportion of patients achieving a confirmed best overall response of CR or PR based on blinded central review according to RECIST 1.1 criteria.
- DOR measured from when earliest CR or PR is observed to PD or death due to any cause based on blinded central review according to RECIST 1.1 criteria.

- Percentage CTS measured from randomization as the sum of diameters based on blinded central review according to RECIST 1.1 criteria.

Phase 2 exploratory endpoints:

- Values and changes from randomization in humoral and cellular immunogenicity data including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine-specific cytokine levels and regulatory and effector T and B cells.
- Values and changes from randomization in serum prediction markers of tumor progression.
- Values and changes from randomization in Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth.
- Values and changes in intra-tumor T cells and biochemical markers from pre- and post- treatment tumor biopsies.

Phase 2 Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs), Grade 3 / 4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study treatment discontinuation.
- Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities.
- Changes and shifts from randomization in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters.
- Change from randomization in ECOG performance grade.
- Concomitant medication use.
- Treatment compliance.

Phase 2 Dose Escalation Primary Endpoint:

- The safety and tolerability of IMU-131 will be evaluated by adverse events (AEs) and laboratory measurements. AEs and laboratory abnormalities will be graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 including:
    - Incidence of treatment-emergent adverse events (TEAEs), Grade 3 / 4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study treatment discontinuation.
    - Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities.
    - Changes and shifts in clinical laboratory, vital signs, and electrocardiogram (ECG) parameters.

Phase 2 Dose Escalation Secondary Endpoints:

- OS measured from enrollment to death due to any cause.
- PFS measured from enrollment to date of earliest progressive disease (PD) based on Investigator disease assessment according to RECIST 1.1 criteria, or to date of death from any cause.

- TTP measured from enrollment to date of earliest PD based on Investigator disease assessment according to RECIST 1.1 criteria.
- ORR measured from enrollment as the proportion of patients achieving a confirmed best overall response of CR or PR based on Investigator disease assessment according to RECIST 1.1 criteria.
- DOR measured from enrollment to when earliest CR or PR is observed to PD or death due to any cause based on Investigator disease assessment according to RECIST 1.1 criteria.
- DCR measured from enrollment as the proportion of patients achieving a confirmed best overall response of complete response (CR), partial response (PR) or stable disease (SD) based on Investigator disease assessment according to RECIST 1.1 criteria.
- Percentage CTS measured from enrollment as the sum of diameters based on Investigator disease assessment according to RECIST 1.1 criteria.

Phase 2 Dose Escalation Exploratory Endpoints:

- Values and changes from enrollment in humoral and cellular immunogenicity data including P467-specific antibodies (IgG), Her-2-specific antibodies (IgG), vaccine- specific cytokine levels and regulatory and effector T and B cells.
- Values and changes from enrollment in serum and biochemical markers of tumor progression.
- Values and changes from enrollment in Her-2-specific antibodies (IgG) inhibition of in-vitro tumor cell growth.
- Values and changes from enrollment in intra-tumor T cells and biochemical markers from pre- and post- treatment tumor biopsies.

3. STUDY DESIGN

This protocol for patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or GEJ has a 2-part design.

Part 1 consists of Phase 1b: Dose Escalation

Phase 1b is an open-label, single arm, dose escalation study to evaluate safety, tolerability and immunogenicity and to assess the RP2D of IMU-131 initiated 14 days prior to the start of chemotherapy. The first dose cohort will be administered 3 doses of 10µg IMU-131, the second dose cohort will be administered 3 doses of 30µg IMU-131 and the third dose cohort will be administered 3 doses of 50µg IMU-131. All patients entering the Phase 1b study will receive IMU-131 and chemotherapy. RP2D is defined as the dose resulting in the best safety/tolerability and immunology results and will be determined after all dose cohorts have completed Day 56 of the study and an interim analysis of the Phase 1b data has been conducted by the CRC.

Phase 1b follows a standard and well validated dose escalation methodology. Review of toxicity data will be conducted by the CRC as soon as each dose level cohort has completed chemotherapy cycle 1 (35 days of the study, including 3 doses of IMU-131) to ensure

ongoing scrutiny of the IMU-131 safety profile. Phase 1b dose escalation will involve 3 dose levels of IMU-131 within a standard 3+3 scheme for determination of safety prior to dose escalation to next dose cohort. Within the 3+3 scheme if the CRC determines there is no dose-limiting toxicity (DLT) for any of the 3 patients in a dose cohort then only 3 patients will enter this cohort before the next dose cohort is opened to recruitment. However if 1 of 3 patients in a cohort has a DLT event then an additional 3 patients will be enrolled at the existing dose level for further evaluation of this dose by the CRC (see Section 10.1.2 Phase 1b Dose Escalation for full details). If there is a single DLT event in each dose cohort before escalation to the next dose cohort then it is possible for a maximum of 18 patients (6 per dose cohort) to be enrolled in the phase 1b study.

Cohort Expansion and RP2D Definition for Phase 1b Study

Dose cohorts in the phase 1b study will be expanded according to a 3+3 safety evaluation design by CRC decision according to the DLT rules presented in Section 10.1.2. This design allows for up to 6 patients per dose cohort for a maximum of 18 patients enrolled in the study. Alternatively, once 3 patients on a single dose have been reviewed and the CRC has given approval to proceed to the next dose cohort then the previous dose cohort may be expanded up to 5 patients per cohort to allow for more thorough evaluation of safety or immunogenicity. Additional recruitment resulting in up to 5 patients per cohort for further safety and immunogenicity evaluation will be at the Sponsor's discretion.

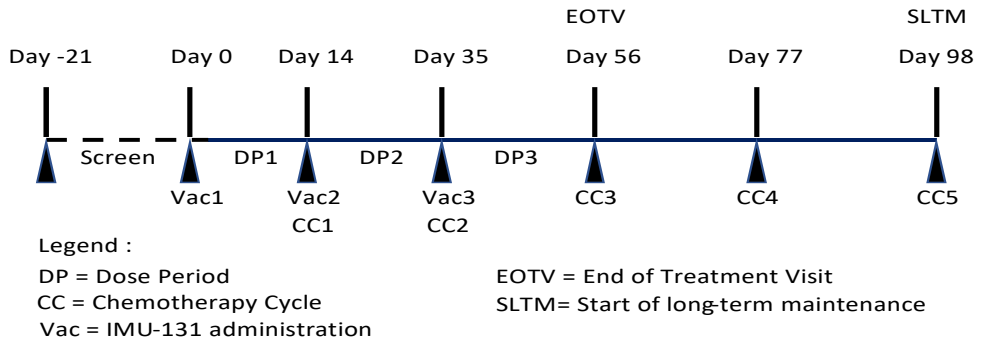
The open-label conduct of Phase 1b allows for rapid assessment of the drug-relatedness status of any toxicity thereby permitting fast and accurate patient safety evaluation.

Phase 1b is a multicenter study with up to 18 patients enrolled. Only 15% - 25% of patients with ACS test positive for HER2/neu over expression, and of these patients it is expected 50% will consent and be eligible for Phase 1b. Thus, approximately 180 patients will be screened for Phase 1b.

A total of 3 injections of IMU-131 (P467-CRM – Montanide emulsion) at the specified dose will be given to patients (on Days 0, 14, and 35), with chemotherapy cycles every 21 days starting from Day 14. Chemotherapy will be ceased by the investigator when clinically indicated for the care of the patient. Patients will be discontinued from the study and cease IMU-131 vaccinations when there is documented evidence of disease progression according to the RECIST 1.1 or if unacceptable toxicity occurs (see Section 6.5 Patient Withdrawal for complete discontinuation criteria).

For a representation of the timeline of events in Phase 1b see Figure 1: Timeline for Phase 1b and for a flow diagram of Phase 1b see Appendix 1: Flow Diagram of Phase 1b.

Figure 1: Timeline for Phase 1b



Phase 1b Long Term Maintenance

Patients completing the Day 56/End of Treatment Visit for Phase 1b will be maintained on booster doses of IMU-131 starting from Day 98. A Long Term Maintenance visit will occur every 12 weeks and consist of a booster vaccination, a urine pregnancy test, collection of blood samples for hematology, serum chemistry and titer kinetic evaluation, a physical examination including vital signs (BP, pulse and temperature), a radiographic assessment and collection of adverse event and concomitant medication data until the patient is no longer participating in long-term maintenance, or IMU-131 has been shown to be of no clinical benefit, its development is discontinued or the Sponsor decides to terminate the study prematurely. Patients will be discontinued from long term maintenance when there is documented evidence of disease progression according to RECIST 1.1 or if unacceptable toxicity occurs.

For details of the procedures and timing of visits during Long Term Maintenance see Table 2: Schedule of Activities Long Term Maintenance.

Humoral and cellular immunogenicity data will include P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) in serum samples and vaccine-specific cytokine levels as well as analysis of regulatory and effector T and B cells will continue to be collected when booster vaccinations are given (i.e. every 12 weeks) during long-term maintenance. The dose of booster vaccinations will be determined and vaccination interval confirmed by the titer kinetics evaluated in Phase1b.

Part 2 consists of Phase 2: Evaluation of exploratory clinical activity of IMU-131

Phase 2 will enroll 36 patients and be conducted in the same centers with the addition of new centers, as required, to fulfill recruitment. Phase 2 will have similar inclusion/exclusion criteria and be conducted according to a similar schedule of events and study procedures. During conduct of the Phase 1b study and prior to the start of Phase 2, an amendment to the current protocol will be submitted for ethical and regulatory review. The Phase 2 evaluation of clinical activity of IMU-131 will be initiated after approval of

Phase 2 and upon completion of Phase 1b (all cohorts completed through Day 56 and selection of a RP2D of IMU-131).

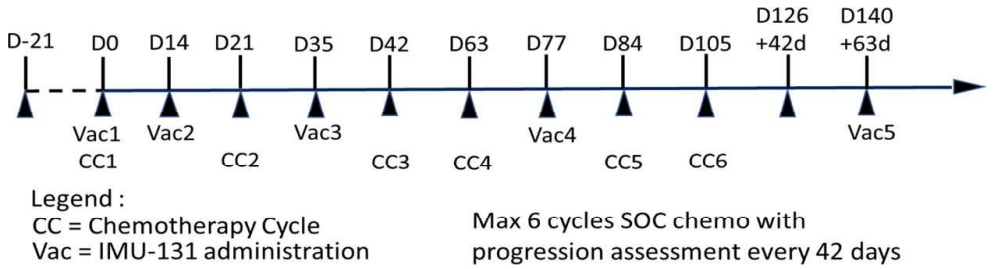
Phase 2 is an open-label randomized comparison of IMU-131 plus standard of care chemotherapy versus standard of care chemotherapy alone. Patients will be randomly assigned to either 'IMU-131 plus chemotherapy' or 'chemotherapy alone' groups. Treatment for both groups will begin at the Baseline/Day 0 visit.

The IMU-131 plus chemotherapy group will receive vaccination of IMU-131 at Baseline/Day 0, Day 14, Day 35, Day 77, Day 140 and then every 63 days until disease progression. Both the IMU-131 plus chemotherapy group and the chemotherapy alone group will receive chemotherapy starting at the Baseline/Day 0 Visit and then every 21 days for a maximum of 6 cycles as clinically indicated or until disease progression, whichever occurs sooner.

The IDMC will be scheduled to meet after 8, 16 and 24 progression events occur and at intervals no less than once per year. Further details of the IDMC meetings and review procedures will be contained in the IDMC charter.

For a representation of the timeline of events in Phase 2 see Figure 2: Timeline for Phase 2 and for a flow diagram of Phase 2 see Appendix 6: Flow Diagram of Phase 2.

Figure 2: Timeline for Phase 2



Phase 2 Extension

The dose escalation during Phase 2 continues the exploration of clinical activity of IMU-131 and is an open-label, multicenter, single arm dose escalation study with the same inclusion/exclusion criteria as Phase 2 and the same schedule of assessments as Phase 2 IMU-131+chemotherapy arm. The safety of each dose will be assessed by CRC after at least 3 patients have 3 doses of IMU-131 and one cycle of chemotherapy and have completed the 35 day DLT window. Two dose cohorts, consisting of 100µg and 200µg doses of IMU-131, will further characterize the safety, immunogenicity, and clinical activity of IMU-131 in combination with chemotherapy.

Phase 2 dose escalation study will be conducted in Georgia, Serbia, and Ukraine with an approximate duration of 24 months: 15 months for recruitment and approximately 12 months on study.

The Sponsor may close the study once the last patient completes the end of treatment visit.

4. PATIENT STUDY ENROLMENT AND DISCONTINUATION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a patient.

4.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Patient has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines;
2. Age $\geq$ 20 years old;
3. Life expectancy of at least 12 weeks;
4. **Phase 1b:** No prior chemotherapy or radiotherapy for advanced gastric or GEJ cancer within 6 months prior to Day 0;
5. **Phase 2/Phase 2 Extension:** No prior chemotherapy or radiotherapy for advanced gastric or GEJ cancer within 3 months prior to Day 0;
6. Metastatic gastric or GEJ adenocarcinoma, or locally advanced disease not amenable to surgical resection;
7. HER2/neu overexpression (3+ by immunohistochemistry (IHC) or if IHC 2+ confirmed by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic in situ hybridization [CISH]). Patients with IHC 2+ expression without confirmation of overexpression by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic in situ hybridization [CISH]) may be included in Phase 1b with agreement of Imugene Limited;
8. **Phase 1b:** ECOG performance status 0–1;
9. **Phase 2/Phase 2 Extension:** ECOG performance status 0–2;
10. At least one measurable lesion as defined by RECIST 1.1 criteria. Patients with non-measurable lesions may be included in Phase1b with agreement of Imugene Limited.;
11. Adequate left ventricular ejection function at baseline, defined as LVEF > 50% by echocardiogram or MUGA scan (Multi Gated Acquisition Scan);
12. Adequate hematologic function: absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L, platelet count $\geq$ 100 x 10^9/L, and hemoglobin $\geq$ 9 g/dL;
13. Adequate liver function evidenced by bilirubin $\leq$ 1.5 x laboratory upper limit of normal [ULN], and ALT and AST $\leq$ 3 x laboratory ULN if no liver involvement or ALT and AST $\leq$ 5 times laboratory ULN with liver involvement;
14. Adequate renal function (creatinine $\leq$ 1.5 x laboratory ULN);

15. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
16. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days following chemotherapy or 180 days after the last dose of IMU-131 (see Section 4.3 for details). A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Previous treatment with trastuzumab or any other HER2/neu targeting antibody or agent;
2. Continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 4 weeks prior to first dose of study treatment. Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted in the absence of active auto-immune disease;
3. Prior organ transplant;
4. **Phase 1b:** Patient not considered a candidate for 5-FU, capecitabine, or cisplatin chemotherapy;
5. **Phase 2/Phase 2 Extension:** Patient not considered a candidate for 5-FU, capecitabine, cisplatin or oxaliplatin chemotherapy;
6. History of documented congestive heart failure; angina pectoris requiring antianginal medication; evidence of transmural infarction on ECG; poorly controlled hypertension; clinically significant valvular heart disease; high risk uncontrolled arrhythmias; or New York Heart Association (NYHA) class II heart disease;
7. If on warfarin (Coumadin®) or other vitamin K antagonists;
8. Concurrent active malignancy except for adequately controlled limited basal cell carcinoma of the skin;
9. Peripheral neuropathy or hearing loss of NCI CTCAE Grade $\geq$ 2;
10. History of uncontrolled seizures, central nervous disorders or psychiatric disability judged by the investigator to be clinically significant and precluding informed consent, participation in the study, or adversely affecting compliance to study drugs;
11. Active infection requiring IV antibiotics;
12. Positive for human immunodeficiency virus (HIV) (HIV 1/2 antibodies) or active hepatitis B (HBsAg reactive) or active hepatitis C (HCV ribonucleic acid [RNA] qualitative) infection;
13. Pregnant or lactating females;
14. Major surgery within 4 weeks prior to study entry. Minor surgery (excluding diagnostic biopsy) within 1 week prior to study entry;

15. Has received a live-virus vaccination within 4 weeks of first study vaccination. Seasonal flu vaccines that do not contain live virus are permitted;
16. Current or recent (within 4 weeks of first IMU-131 vaccination) treatment with another investigational drug or participation in another investigational study.
17. **Phase 2/Phase 2 Extension:** Patients with a known diphtheria toxoid hypersensitivity.

4.3. Contraception Guidelines

All male and female patients who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days following chemotherapy or 180 days after the last dose of IMU-131. The investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, injected or implanted hormonal methods of contraception
2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

In Phase 1b patients will be allocated to treatment in a non-randomized, sequential order. Each patient will be administered 3 injections of IMU-131 (P467-CRM197-Montanide emulsion), at a single dose level on Days 0, 14, and 35, accompanied by chemotherapy cycles every 21 days starting from Day 14.

In Phase 2, patients who are determined to be eligible for the study will be randomized on their Baseline/Day 0 Visit. Patients will be allocated to receive IMU-131 plus chemotherapy or chemotherapy only in a 1:1 ratio. Randomization will be performed centrally and stratified by tumor stage at screening (III vs IV)

Patients will be randomized into this open-label study using an Interactive Voice or Web Response System (IxRS). The central radiography review will be blinded. The rules describing the distribution of data and results will be documented prior to study commencement.

The Phase 2 dose escalation study is an open label and non-randomized with patients entering the study sequentially according to the dose level being studied.

5.2. Vaccine Supplies

[redacted]

The Quality Control Standards and Requirements for the aqueous phase vaccine (P467-CRM197) and the adjuvant (Montanide ISA 51 VG) are described in separate release protocols/Certificate of Analysis and the required approvals have been obtained.

5.2.1. Formulation and Packaging

The investigational product, IMU-131, will be supplied as P467-CRM197 (aqueous phase vaccine) and Montanide ISA 51 VG (adjuvant) in separate boxes. Each box of P467-CRM197 contains 1 vial of 200 µg aqueous phase vaccine in 1 mL PBS buffer, two vial adapters, two luer-lock syringes, one dosing syringe and needle and one I connector. Each box of Montanide contains a single 3 mL vial of Montanide ISA 51 VG.

Chemotherapy is a standard of care treatment and will be sourced and stored by Pharmacy under usual and standard conditions.

5.2.2. Preparation and Dispensing

Emulsification of IMU-131 vaccine (P467-CRM197) – adjuvant (Montanide ISA 51 VG) mixture will be completed by appropriately trained and qualified pharmacy or site staff. Training and qualification will be provided by the Sponsor or their delegate and documented in the study file.

[redacted]

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Phase 1b

In Phase 1b, IMU-131 is formulated into either a low, medium or high dose with the concentration of each dose remaining constant while the injection volume varies:

- Low dose: 10 µg (peptide P467 antigen equivalent) P467-CRM197 in 50 µL PBS buffer and 50 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.1mL injection volume;
- Mid dose: 30 µg (peptide P467 antigen equivalent) P467-CRM197 in 150 µL PBS buffer and 150 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.3mL injection volume or;
- High dose: 50 µg (peptide P467 antigen equivalent) P467-CRM197 in 250 µL PBS buffer and 250 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.5mL injection volume.

In Phase 1b, chemotherapy will be prepared and dispensed according to Pharmacy standard practice. Chemotherapy will include the following treatments:

- cisplatin, IV (80 mg/m^2) and either;
- 5-FU, 4000 mg/m^2 continuous infusion;
- or capecitabine, 2000 mg/m^2/day, orally.

Phase 2

In Phase 2, injections of IMU-131-Montanide emulsion (IMU-131) at 50 µg consisting of 50 µg (peptide P467 antigen equivalent) P467-CRM197 in 250 µL PBS buffer and 250 µL Montanide ISA 51 Sterile adjuvant resulting in a 0.5mL injection volume, will be given to patients in the 'IMU-131 plus chemotherapy' group on Days 0, 14, 35, 77, 140 and then every 63 days until disease progression.

In Phase 2, chemotherapy will be prepared and dispensed according to Pharmacy standard practice. Chemotherapy will include the following treatments:

- cisplatin, IV (80 mg/m^2) and either 5-FU, 4000 mg/m^2 continuous infusion or capecitabine, 2000 mg/m^2/day, orally;
- Or oxaliplatin, IV (130 mg/m^2) and capecitabine, 2000 mg/m^2/day, orally.

Phase 2 Extension

In Phase 2 dose escalation, IMU-131-Montanide emulsion (IMU-131 vaccine) is formulated into a 100 µg dose in a 1.0 mL injection volume by mixing 100 µg (peptide P467 antigen equivalent) P467-CRM197 in 500 µL PBS buffer with 500 µL Montanide ISA 51 sterile adjuvant resulting in a 1.0 mL injection volume.

- Cohort 1 will be dispensed 100 µg IMU-131-Montanide emulsion.
- Cohort 2 will be dispensed 200 µg IMU-131-Montanide emulsion.

Refer to the study pharmacy manual for detailed IMU-131 vaccine preparation and administration instructions.

In Phase 2 Extension, chemotherapy will be prepared and dispensed according to Pharmacy standard practice. Chemotherapy will include the following treatments:

- cisplatin, IV (80 mg/m^2) and either 5-FU, 4000 mg/m^2 continuous infusion or capecitabine, 2000 mg/m^2/day, orally;
- Or oxaliplatin, IV (130 mg/m^2) and capecitabine, 2000 mg/m^2/day, orally.

5.2.3. Administration

Chemotherapy is to be administered according to institution standard practice including all pre-medications, concomitant medications and dosing criteria. Dose adjustments and delays, and discontinuation based on AEs, patient's condition, and cumulative toxicities are permitted for the clinical care of the patient at the discretion of the investigator.

Body weight will be determined prior to the start of treatment. Body surface area (BSA: based on weight and baseline height) will be calculated prior to starting each 21-day chemotherapy cycle. Dose modification will be required for >10% change in BSA, unless investigator considers this not appropriate.

Chemotherapy will be administered in 21-day cycles as tolerated or for any other reason to discontinue chemotherapy treatment as determined by the investigator for the clinical care of the patient.

Phase 1b

IMU-131 administration:

Patients will be enrolled in cohorts of up to 6 patients at one of three escalating dose levels of IMU-131:

- Cohort 1 - 10 µg as a 0.1 mL injection
- Cohort 2 - 30 µg as a 0.3 mL injection
- Cohort 3 - 50 µg as a 0.5 mL injection

The IMU-131 vaccine will be administered IM into the deltoid region of the upper arm with a 0.60 x 25 mm 23G needle on Days 0, 14 and 35.

Chemotherapy administration:

Standard of care chemotherapy will be administered as a concomitant treatment to all patients as a 21-day regimen starting 14 days after first IMU-131 vaccination. To document compliance while away from the clinic, patients will record capecitabine treatment in a patient diary.

Chemotherapy will include the following treatments, the dose and duration of which may be varied by the investigator as clinically indicated for the patient: cisplatin, IV (80 mg/m^2 on Day 14, then every 21 days) and either 5-FU, 4000 mg/m^2 as continuous infusion (CIV, administered as 1000 mg/m^2/day for 96 hours on days 14 to 17, then every 21 days) or capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 14 to 27, then every 21 days).

Phase 2

IMU-131 administration:

Patients in the 'IMU-131 plus chemotherapy' group will receive injections of IMU-131 at 50µg in a 0.5mL injection volume on Days 0, 14, 35, 77, 140 and then every 63 days until disease progression.

Phase 2 Extension

IMU-131 administration:

A total of 3 injections of IMU-131-Montanide emulsion (IMU-131 vaccine) at a particular dose will be given to patients in the Phase 2 dose escalation study on Days 0, 14, and 35, and then every 63 days with chemotherapy cycles every 21 days (to a maximum of 6 cycles) starting from Day 0 prior to safety assessment by CRC.

The IMU-131 vaccine will be administered IM into the deltoid region of the upper arm with a 25-38mm (1-1.5 inches), 21-23G needle.

Refer to the study pharmacy manual for detailed IMU-131 vaccine preparation and administration instructions.

Chemotherapy administration in Phase 2 and Phase 2 Extension:

Patients in both the IMU-131 plus chemotherapy group and the chemotherapy alone group will receive chemotherapy starting at the Baseline/Day 0 Visit and then every 21 days for a maximum of 6 cycles as clinically indicated or until disease progression, whichever occurs sooner. One or more chemotherapy treatments may be varied by dose, frequency or discontinued completely as determined by the investigator for the clinical care of the patient.

Chemotherapy will be administered as a concomitant therapy to all patients as a 21-day regimen starting at Day 0 and consisting of: cisplatin by intravenous administration at 80 mg/m^2 on the first day of each cycle and either 5-FU, 4000 mg/m^2 CIV (administered as 1000 mg/m^2/day as continuous infusion for 96 hours on days 1 to 4 of each cycle) or capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 1 to 14 of each cycle), or oxaliplatin, by intravenous administration at 130 mg/m^2 on Day 1 of each cycle and capecitabine for 14 days at 2000 mg/m^2/day, orally (administered as 1000 mg/m^2 twice daily morning and evening for a total of 2000 mg/m^2/day on days 1 to 14 of each cycle).

5.2.4. Compliance

Study site staff are responsible for administration of IMU-131. To monitor compliance, confirmation of successful emulsification by droplet test will be documented prior to each administration of IMU-131 and the exact volume and dose administered will be recorded in the CRF.

To document compliance while away from the clinic, patients will record capecitabine treatment in a patient diary.

5.3. Drug Storage and Drug Accountability

The vaccine and adjuvant must be stored in a safe and locked place with no access for unauthorized personnel.

The peptide antigen P467-CRM197 must be kept frozen until use in a freezer (< -15ºC).

The adjuvant Montanide ISA 51 VG must be stored in a refrigerator at + 2 - + 8ºC.

Storage conditions stated in the Investigator Brochure (IB) may be superseded by the label storage conditions. Ensure the label is always checked for correct storage conditions.

After approval from Imugene Limited, both used and unused vaccine and adjuvant vials will be sent for destruction. The destruction may be performed at the study site using locally approved biosafety procedures and documentation.

5.4. Concomitant Medication(s)

5.4.1. Permitted medications

Participants will follow their oncology care plan. All medications required as part of a participant's normal clinical care for support of their medical conditions are permitted during the study, with the exception of prohibited medications listed in Section 5.4.2. All concomitant medications must be recorded in the source documentation and in the CRFs for the duration of patient participation.

Treatment with an oral corticosteroid, such as dexamethasone, up to 8 mg daily (24mg maximum) during each chemotherapy cycle is allowed if required but may impact the development of Her2/neu antibodies.

5.4.2. Prohibited medications

The following medications/treatments are prohibited during the study:

- Other investigational drug;
- Continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive or immuno-modulatory medications unless required to treat an immune adverse event. Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted;
- Total doses greater than 24mg dexamethasone equivalent of oral corticosteroids per chemotherapy cycle are prohibited.

6. STUDY PROCEDURES

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. Every attempt should be made to complete all study visits as outlined in the Schedule of Activities. All missed study visits and visits outside the visit window are considered protocol deviations.

Please refer to Table 1 Schedule of Activities: Phase 1b which lists the visits, permissible visit windows and required study procedures.

For details of the procedures and timing of visits during Long Term Maintenance see Table 2: Schedule of Activities Long Term Maintenance.

Please refer to Table 3 Schedule of Activities: Phase 2 and Phase 2 Extension, which lists the visits, permissible visit windows and required study procedures.

6.1. Screening (Phase 1b and Phase 2/Phase 2 Extension)

Patients agreeing to participate in the study will sign the informed consent documents. A patient screening number comprised of a unique site number and sequential screening number will be issued at the time of consent. The reason for all screen failures will be documented. The screening assessments should occur within 3 weeks prior to starting treatment.

Screening will occur across at least 2 clinic visits. At the first screening visit the patient will be asked to provide consent, the inclusion/exclusion criteria will be checked and screening for HER2/neu overexpression will be completed. All other screening procedures will be conducted at subsequent screening visits.

Procedures will be performed in the following order.

A) First screening visit:

- Obtain Informed Consent;
- Check inclusion/exclusion criteria;
- Use archival tissue, previous HER2 overexpression results or obtain biopsy for HER2 overexpression confirmation and intra-tumor markers.

B) Subsequent screening visits:

- Medical history (including cancer history), prior and concomitant medications and procedures, and demographics will be documented;
- Physical examination;
- Height, weight, and vital signs (blood pressure, temperature and heart rate);
- ECOG performance score;
- Radiographic assessment (for Baseline assessment, allowed up to 14 days prior to Day 0);
- Cardiac assessment by echocardiography or MUGA scan and 12-lead ECG;
- Urine pregnancy test (female);
- Blood sample for hematology, serum chemistry, HIV and hepatitis B and C;
- Blood sample for cellular immunology (Phase 2 Extension only).

If a patient's laboratory results do not meet the eligibility criteria at Screening, the laboratory assessment may be repeated within the Screening Period.

6.1.1. Re-Screening

Phase 1b

Patients are able to be re-screened when the following situations are present: Dose cohort not open; Drug supply not available at site; Unable to attend/schedule first dose visit; Tests or procedures are not completed in screening period (i.e., patients who miss their 21-day screening window). For any other situation, agreement must be obtained from Imugene Limited before performing re-screening.

If a patient has been entered in the CRF as a "screen failure" they cannot be re-screened.

A new ICF must be signed before re-screening can commence. Re-screened patients will keep the same subject number. Screening procedures and test results/eligibility checks will be updated as part of re-screening.

Phase 2/Phase 2 Extension

Patients may be re-screened when the following situations are present: Drug supply not available at site; Unable to attend/schedule first dose visit; Tests or procedures are not completed in screening period (i.e., patients who miss their 21-day screening window). For any other situation, agreement must be obtained from Imugene Limited before performing re-screening.

Patients who have been randomized cannot be re-screened.

A new ICF must be signed before re-screening can commence. Re-screened patients will keep the same screening number. Screening procedures and test results/eligibility checks will be updated as part of re-screening.

Only Serious Adverse Events (SAEs) caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported from date of first informed consent to initiation of study drug(s).

6.2. Phase 1b Study Period

6.2.1. Phase 1b Vaccination procedure (Day 0, 14 and 35)

All vaccinations must be administered in an appropriate medical facility equipped for immediate intervention in the event of an allergic reaction.

Preparation of IMU-131 is to be conducted precisely according to instruction in Section 5.2.2 Preparation and Dispensing. Patients will be vaccinated on days 0, 14 and 35 respectively. Prior to vaccination patients will undergo complete physical examinations, including vital signs (blood pressure, pulse, temperature). IMU-131 vaccine should be administered intramuscularly (IM) into the deltoid region of the upper arm with a 0.60 x 25 mm 23G needle. The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol) prior to vaccination of study drug IM. The vaccine must not be injected into blood vessels and the Medical Professional administering the injection must confirm IM placement via a "negative" blood return on a "pull back" check before injecting IMU-131.

Patients will be observed for at least 30 minutes after vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration. Any reactions that occur during this time must be recorded by the investigator in the CRF. Thirty minutes (+/- 10 min) after vaccination, the patient's temperature will be recorded.

Patients will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

6.2.2. Phase 1b Dose Period 1 (Day 0 and Day 2)

Dose Period 1 consists of Day 0/Baseline and Day 2. There are no allowable visit windows for Dose Period 1.

Day 0/Baseline procedures will be performed in the following order:

- Physical examination;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Blood sample for hematology and serum chemistry tests;
- Blood sample for immunology tests;
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events.

Day 2 procedures will be performed in the following order:

- Vaccination site evaluation for local effects;
- Record concomitant treatments;
- Record adverse events.

6.2.3. Phase 1b Dose Period 2 (Day 14 and Day 16)

Dose Period 2 consists of Day 14 and Day 16. The visit window for Dose Period 2 is +/- 3 day of the scheduled visit.

Day 14 procedures will be performed in the following order:

- Physical examination;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Blood sample for hematology and serum chemistry tests;
- Blood sample for immunology tests;

- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 1.

Day 16 procedures will be performed in the following order:

- Vaccination site evaluation for local effects;
- Record concomitant treatments;
- Record adverse events.

6.2.4. Phase 1b Dose Period 3 (Day 35 and Day 37)

Dose Period 3 consists of Day 35 and Day 37. The visit window for Dose Period 3 is +/- 3 days of the scheduled visit.

Day 35 procedures will be performed in the following order:

- Physical examination;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Blood sample for hematology and serum chemistry tests;
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 2.

Day 37 procedures will be performed in the following order:

- Vaccination site evaluation for local effects;
- Record concomitant treatments;
- Record adverse events.

6.2.5. Phase 1b End of Treatment Visit (Day 56)

The end of treatment visit occurs on Day 56. The allowable visit window for this visit is +/- 3 days.

End of treatment/Day 56 procedures will be performed in the following order:

- Physical examination;

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Blood sample for hematology and serum chemistry tests;
- Blood sample for immunology tests;
- Cardiac assessment by echocardiography or MUGA scan and 12-lead ECG;
- Radiographic assessment;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 3.

6.2.6. Phase 1b chemotherapy only visit (Day 77)

Day 77 is for continuation of chemotherapy, as determined by the study investigator. A visit window of +/- 7 days is allowable.

Day 77 procedures will be performed in the following order:

- Physical examination;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Blood sample for hematology and serum chemistry tests;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 4.

6.2.7. Phase 1b Follow-up Post-Withdrawal Visit (30 – 40 days after last vaccination)

A visit window of - 2 days to +16 days is allowable.

When the patient is withdrawn during either Phase 1b or Long Term Maintenance this visit occurs 30 – 40 days after the last vaccination. The subject summary page of the CRF should be completed after this visit has occurred.

Follow-up post withdrawal procedures will be performed in the following order:

- Physical examination;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Record concomitant treatments (medications and procedures);
- Record adverse events.

6.2.8. Phase 1b Unscheduled Visit

Unscheduled visits may be conducted at any time during Phase 1b or Long Term Maintenance by the investigator if clinically indicated for the care of the patient.

An unscheduled visit may include any of the protocol required assessments listed in Section 7: Phase 1b Assessments. The exact assessments conducted at the unscheduled visit will be specified by the investigator and recorded in the CRF. Additional tests and procedures may be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor.

6.3. Phase 1b Long Term Maintenance of Phase 1b patients (Day 98 onwards)

Patients completing the End of Treatment/Day 56 assessment in Phase 1b will move into long term maintenance starting at Day 98. Long term maintenance will continue until the patient is no longer participating in the study, or IMU-131 has been shown to be of no clinical benefit, its development is discontinued or the Sponsor decides to terminate the study prematurely. Patients will discontinue participation in long term maintenance when there is documented evidence of disease progression according to RECIST 1.1 response criteria or if unacceptable toxicity occurs. The last long term maintenance visit prior to discontinuation will be recorded as the end of treatment visit for long term maintenance. The Phase 1b follow-up post withdrawal visit (Section 6.2.7) will be conducted 30 – 40 days after the last vaccination during long term maintenance.

In addition to booster vaccinations most likely every 12 weeks each Long Term Maintenance visit will include a urine pregnancy test, collection of blood samples for hematology, serum chemistry and titer kinetic evaluation, a physical examination including vital signs (BP, pulse and temperature), a radiographic assessment and collection of adverse event and concomitant medication data. For details of the procedures and timing of visits during Long Term Maintenance see Table 2: Schedule of Activities Long Term Maintenance.

Humoral and cellular immunogenicity data will include P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) in serum samples and vaccine-specific cytokine levels as well as analysis of regulatory and effector T and B cells will continue to be collected when booster vaccinations are given (i.e. every 12 weeks) during long-term maintenance. The dose of booster vaccinations will be determined and vaccination interval confirmed by the titer kinetics evaluated in Phase1b, details of which will be provided for ethical and regulatory review as an amendment to this protocol.

6.4. Phase 2 and Phase 2 Extension Study Period

6.4.1. Phase 2 and Phase 2 Extension Vaccination procedure

All vaccinations must be administered in an appropriate medical facility equipped for immediate intervention in the event of an allergic reaction.

Preparation of IMU-131 is to be conducted precisely according to instruction in Section 5.2.2 Preparation and Dispensing. Prior to vaccination patient's vital signs (blood pressure, pulse, temperature) will be measured. IMU-131 vaccine should be administered intramuscularly (IM) into the deltoid region of the upper arm with a 25-38mm (1-1.5 inches), 21-23G needle needle. The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol) prior to vaccination of study drug IM. The vaccine must not be injected into blood vessels and the Medical Professional administering the

injection must confirm IM placement via a "negative" blood return on a "pull back" check before injecting IMU-131.

Patients will be observed for at least 30 minutes after vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration. Any reactions that occur during this time must be recorded by the investigator in the CRF. Thirty minutes (+/- 10 min) after vaccination, the patient's temperature will be recorded.

Patients will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

6.4.2. Phase 2 and Phase 2 Extension Baseline/Day 0

There is no allowable visit window for Baseline/Day 0. Day 0/Baseline procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry (Screening safety lab samples taken within 72 hours of first study treatment do not need to be repeated on Day 0);
- Blood sample for humoral and cellular immunology;
- Blood sample for exploratory endpoints;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- ECOG performance score;
- Radiographic assessment (Allowed during screening period - up to 14 days prior to Day 0)
- Administer IMU-131 vaccination and record body temperature 30 (+/-10) minutes after vaccination (only for patients in IMU-131 plus chemotherapy group);
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 1.

6.4.3. Phase 2 and Phase 2 Extension Week2/Day 14 (only for patients in IMU-131 plus chemotherapy cohorts)

The visit window for Day 14 is +/- 3 days of the scheduled visit. Day 14 procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;

- Record concomitant treatments;
- Record adverse events.

6.4.4. Phase 2 and Phase 2 Extension Week 3/Day 21

The visit window for Day 21 is +/- 3 days of the scheduled visit. Day 21 procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry;
- Blood sample for humoral immunology;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 2.

6.4.5. Phase 2 and Phase 2 Extension Week 5/Day 35 (only for patients in IMU-131 plus chemotherapy cohorts)

The visit window for Day 35 is +/-3 days of the scheduled visit. Day 35 procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events.

6.4.6. Phase 2 and Phase 2 Extension Week 6/Day 42

The visit window for Day 42 is +/- 3 days of the scheduled visit. Day 42 procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry;
- Blood sample for humoral immunology;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- Radiographic assessment;
- Record concomitant treatments;

- Record adverse events;
- Initiate chemotherapy cycle 3.

6.4.7. Phase 2 and Phase 2 Extension Week 9/Day 63

The visit window for Day 63 is +/- 7 days of the scheduled visit. Day 63 procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry;
- Blood sample for humoral immunology;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 4.

6.4.8. Phase 2 and Phase 2 Extension Week 11/Day 77 (only for patients in IMU-131 plus chemotherapy cohorts)

The visit window for Day 77 is +/- 7 days of the scheduled visit. Day 77 procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events.

6.4.9. Phase 2 and Phase 2 Extension Week 12/Day 84 (Repeat every 12 weeks/84 days)

The visit window for Day 84 is +/- 7 days of the scheduled visit. Day 84 procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Blood sample for hematology and serum chemistry;
- Blood sample for humoral and cellular immunology;
- Blood sample for exploratory endpoints;
- Urine pregnancy test (female);
- Physical examination;
- ECOG performance score;

- Cardiac assessment by echocardiography or MUGA scan and 12-lead ECG;
- Radiographic assessment;
- Optional tumor biopsy sample (at Day 84);
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 5.

6.4.10. Phase 2 and Phase 2 Extension Week 15/Day 105

The visit window for Day 105 is +/- 7 days of the scheduled visit. Day 105 procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- Record concomitant treatments;
- Record adverse events;
- Initiate chemotherapy cycle 6.

6.4.11. Phase 2 and Phase 2 Extension Week 18/Day 126 (Repeat every 12 weeks/84 days)

The visit window for Day 126 is +/- 7 days of the scheduled visit. Day 126 procedures should be performed in the following order:

- Blood sample for hematology and serum chemistry;
- Blood sample for humoral immunology;
- Weight, and vital signs (blood pressure, temperature and heart rate);
- Urine pregnancy test (female);
- Physical examination;
- Radiographic assessment;
- Record concomitant treatments;
- Record adverse events;

6.4.12. Phase 2 and Phase 2 Extension Week 20/Day 140 (Repeat every 9 week/63 days - only for patients in IMU-131 plus chemotherapy cohorts)

The visit window for Day 140 is +/- 7 days of the scheduled visit. Day 140 procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);

- Urine pregnancy test (female);
- Administer IMU-131 vaccination;
- Record body temperature 30 (+/-10) minutes after vaccination;
- Record concomitant treatments;
- Record adverse events.

6.4.13. Phase 2 and Phase 2 Extension End of Treatment (EoT) Visit

When progressive disease or withdrawal from study has been confirmed, the EoT visit will be conducted at least 28 Days (+/- 7) after last dose of study medication. An optional post-progression tumor biopsy sample will be requested from patients and may be provided at any time post progression. EoT visit procedures should be performed in the following order:

- Weight, and vital signs (blood pressure, temperature and heart rate);
- Blood sample for hematology and serum chemistry;
- Blood sample for humoral and cellular immunology;
- Blood sample for exploratory endpoints;
- Urine pregnancy test (female);
- Physical examination;
- ECOG performance score;
- Cardiac assessment by echocardiography or MUGA scan and 12-lead ECG;
- Record concomitant treatments;
- Record adverse events (AEs to be checked at least 28 days after last study treatment per Section 9.2: Reporting Period).

6.4.14. Phase 2 Post-Treatment Follow-up Visit (Every 42 days after EoT visit)

This visit may be conducted via phone, email, review of medical records or via publicly available information. A visit window of +/- 7 days is allowable.

- Radiographic assessment (only for patients who withdrew from study before progressive disease was confirmed);
- Record survival follow-up assessment;
- Record post-study anti-cancer treatment.

6.4.15. Phase 2 and Phase 2 Extension Unscheduled Visit

Unscheduled visits may be conducted at any time during Phase 2 by the investigator if clinically indicated for the care of the patient.

An unscheduled visit may include any of the protocol required assessments listed in Section 8: Phase 2 Assessments. The exact assessments conducted at the unscheduled visit will be specified by the investigator and recorded in the CRF. Additional tests and procedures may

be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor.

6.5. Patient Withdrawal

6.5.1. Main discontinuation criteria

Patients will discontinue study treatment and complete the study according to the study protocol when there is documented evidence of disease progression according to RECIST 1.1 response criteria or if unacceptable toxicity occurs. Patients may discontinue study treatment and be withdrawn from the study prematurely based on symptomatic clinical disease progression without documented radiographic evidence only after discussion with the Sponsor/medical monitor.

6.5.2. Contraindications to repeated vaccination

If any of the following adverse events arise during the study they constitute contraindications to further administration of IMU-131, and patients should discontinue IMU-131 treatment permanently and be withdrawn from the study immediately, with appropriate safety follow-up by the investigator until resolution of the event, as with any adverse event (see Section 9: Adverse Event Reporting):

- Anaphylactic reaction following the administration of vaccine(s).
- Any clinically relevant immunosuppressive or immuno-deficient condition.

The following events constitute contraindications to administration of IMU-131. If an adverse event, the event must be reported and the patient followed as with any adverse event. Withdrawal of patients experiencing the following events is at the discretion of the investigator as indicated below:

- Acute illness at the time of vaccination. Acute illness is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., temperature <38°C. Withdrawal is at the discretion of the investigator if acute illness will not resolve in sufficient time to allow for vaccination schedule to continue.
- Temperature $\geq$ 38°C at the time of vaccination. Withdrawal is at the discretion of the investigator if raised temperature will not resolve in sufficient time to allow for vaccination schedule to continue.

6.5.3. Additional Discontinuation Criteria

Patients must discontinue from the study if any of the following additional criteria are met:

- The patient requests discontinuation from the study;
- The Sponsor stops the study;
- The Sponsor stops the patient's participation in the study;
- The patient becomes pregnant during the study period.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. PHASE 1B ASSESSMENTS

Every effort should be made to ensure that protocol required tests and procedures are completed as described.

7.1. Phase 1b Physical Examination (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)

The physical examination will include an evaluation of body systems (e.g. cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). Evaluation for pre-existing condition that might exclude the patient from eligibility or could interfere with the patient's participation and compliance with the protocol should be performed at Screening.

7.2. Phase 1b Height, Weight and Vital Signs (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)

Body height (at screening visit only), weight, and vital signs (blood pressure, pulse and temperature) will be measured.

7.3. Phase 1b Radiographic Assessment (Screening, Days 56, 98, LTM visits)

For all patients, a radiographic assessment will be performed at Screening (for inclusion criteria assessment), and at Day 56, Day 98 and at long term maintenance visits until disease progression.

Computed Tomography (CT) scan of the chest abdomen and pelvis with contrast should be performed. MRI of the abdomen and pelvis with contract and non-contrast CT chest may be done in patients with iodine contrast dye allergy or if lesions cannot be visualized on CT scan.

Radiographic assessments must be performed within +/- 2 weeks of the planned visit date. Additional radiographic assessment may be performed as part of a Phase 1b Unscheduled

Visit (Section 6.2.8) at the discretion of the investigator as clinically indicated. Assessment of the tumor will include evaluation according to the RECIST 1.1.

7.4. Phase 1b Cardiac Assessment (Screening, Day 56)

Cardiac assessment of suitability for inclusion in the study and on Day 56 will be performed by the study investigator and be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation of left ventricular ejection fraction (LVEF) by echocardiography or MUGA scan. Cardiology consult may be sought by the investigator if required to confirm suitability for inclusion in the study.

7.5. Phase 1b Laboratory Assessments

Hematology and serum chemistry analyses will be performed by an accredited central laboratory. Immunological analysis will be performed by an accredited specialist immunology laboratory.

Central laboratory results should be reviewed by the principal investigator (PI) or another qualified study staff member as soon as received. Subject management is dependent upon close review of the laboratory data.

Unscheduled and repeat laboratory tests will also be performed by the central laboratory. However, if the turnaround time from the central laboratory is not sufficiently rapid for clinical management of the subject, local laboratory test results may be used to make the necessary clinical judgments.

A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping will be provided to all participating sites.

7.5.1. Phase 1b Safety Laboratory Assessments (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)

Blood samples of approximately 10 mL in total for the assessment of hematological and serum chemistry parameters will be collected and processed in accordance with the central laboratory study manual.

All hematology and serum chemistry samples will be submitted by the Investigator to the certified central laboratory for analysis. Blood samples for hematology and serum chemistry will be prepared using standard procedures.

Safety laboratory panels are defined as follows:

Human immunodeficiency virus (HIV 1/2 antibodies), hepatitis B (HBsAg reactive) and hepatitis C (HCV ribonucleic acid [RNA] qualitative) (at screening only).

Hematology: Hematology to include CBC, including RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, C-reactive protein (CRP), IL-1, IL-6, IL8, TNF-a, CXCL-9 and CXCL-10.

Serum Chemistry: BUN or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT.

Abnormalities in clinical laboratory tests that are considered clinically significant by the investigator will be recorded on the laboratory CRF page. If abnormal laboratory results are also considered an adverse event, then a corresponding AE CRF will also be completed. If values after the first dose meet criteria defining them as serious, they must be reported as SAEs (see Section 9.12.1: Serious Adverse Event Reporting Requirements).

7.5.2. Phase 1b Immunologic Assessments (Screening, Days 0, 14, 35, 56, 77, 98, LTM visits)

Prior to each vaccination a 1 x 8 mL whole blood sample for humoral immunity will be obtained from the patient at Days 0, 14, 35, 56, 77, 98 and at LTM visits. Additionally, on Days 0, 56 and at each LTM visit, 5 x 8 mL heparinized blood samples will be collected for PBMC isolation and analysis of cellular parameters.

All blood samples for immunological assessment will be collected and processed at the study site according to the Central Laboratory Manual. These immunological blood samples will be collected by, and stored at, the central laboratory before bulk shipment to the specialist immunology laboratory at the [redacted] for analysis.

7.5.3. Phase 1b HER2/neu overexpression (Screening)

Confirmation of HER2/neu overexpression is required for inclusion in this study. However, patients with IHC HER2 ++ expression without confirmation of overexpression by fluorescent in situ hybridization [FISH] brightfield double *in situ* hybridization [BDISH] or chromogenic in situ hybridization [CISH]) may be included in Phase 1b with agreement of Imugene Limited.

A previous pathology result confirming HER2/neu overexpression is acceptable. If analysis of a tumor biopsy is required for confirmation of HER2/neu overexpression then this may be achieved via analysis of a fresh or archived tissue sample. Results are to be entered into the respective CRF.

If a biopsy sample is used to determine HER2/neu overexpression then analysis of intra-tumor T cells for CD8+, CD4+, Th1, Th2, Tregs (Foxp3+ CD25+) will also be performed if these analyses are available at the pathology lab conducting HER2/neu overexpression analysis.

HER2/neu analysis will be conducted at each center's local pathology laboratory by immunohistochemistry (IHC) and fluorescent *in situ* hybridization [FISH] or chromogenic *in situ* hybridization [CISH] if IHC result is equivocal.

Using the IHC method an unequivocal result of HER2 overexpression is defined as HER2 +++, an equivocal result is defined as HER2 ++, and a negative result is defined as HER2 +. If equivocal result (IHC HER2 ++) then additional analysis via FISH or CISH will be

conducted for confirmation of HER2 overexpression. The definition of FISH or CISH positivity in gastric or gastro–esophageal junction cancer is a HER2: chromosome 17 ratio of ≥2.0.

7.5.4. Phase 1b ECOG performance grade (Screening)

The ECOG performance grade for screening evaluation should be determined using the criteria defined in Appendix 3: ECOG Performance Status Scale.

7.6. Phase 1b Vaccination site evaluation (Days 2, 16, 37)

The purpose of vaccination site evaluation is to determine the nature and frequency of local/vaccination site reactions. The vaccination site should be evaluated for local effects of the vaccine injection including pain, tenderness, erythema/redness and swelling/induration (see Section 9.7.1 Local (injection site) Adverse Event Intensity for further details). All local vaccination site effects are to be reported in the CRF and graded according to Table 4: Grading of Local Adverse Event Intensity presented in Section 9.7.1.

Photographs will be taken during vaccination site evaluation if there are visible local injection site reactions.

7.7. Phase 1b Pregnancy Test (Screening, Days 0, 14, 35, 98, LTM visits)

For female patients of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of each vaccine dose. A negative pregnancy test result is required before the patient may receive the investigational product. If urine pregnancy test is positive then confirmation of pregnancy will be by BHCG blood test. If BHCG blood test is negative then vaccination schedule may resume. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

8. PHASE 2 AND PHASE 2 EXTENSION ASSESSMENTS

Every effort should be made to ensure that protocol required tests and procedures are completed as described.

8.1. Assessments via Telemedicine

Telemedicine uses advanced telecommunication technologies to exchange health information and provide health care services across geographic, social, and other barriers. Where circumstances allow, and where additional flexibility is required due to restricted patient access to the study clinic or personnel, telemedicine technology may be used to collect study data to supplement study assessments. For example, visits may be conducted over several days within each visit window, with suitable assessments being completed using telemedicine technology with the remaining assessments being completed during a physical clinic visit. Examples of study assessments which may be completed using telemedicine technology include documenting concomitant treatments and adverse events, ECOG performance grade, and survival follow-up.

8.2. Phase 2 and Phase 2 Extension Physical Examination (Screening, Baseline, Days 21, 42, 63, 84, 105, 126 then every 42 days and EoT visit)

The physical examination will include an evaluation of body systems (e.g. cardiovascular, gastrointestinal, neurological, head and neck, respiratory, dermatology). After the Baseline physical examination, a symptom-directed physical examination is allowed at subsequent visits at the investigator's discretion.

8.3. Phase 2 and Phase 2 Extension Height, Weight, Vital Signs, Concomitant Medications, Concomitant Procedures and Adverse Events (at each study visit, excluding post-treatment follow-up visits)

Body height (at screening visit only), weight, and vital signs (blood pressure, pulse and temperature) will be measured and concomitant medications, concomitant procedures and adverse events will be documented.

8.4. Phase 2 and Phase 2 Extension Radiographic Assessment (Baseline, Days 42, 84, 126 then every 42 days)

For all patients a radiographic assessment will be performed at Baseline (assessment allowed up to 14 days before Baseline Visit), Days 42, 84, 126 then every 42 days until disease progression. Assessment of the tumor will include evaluation according to RECIST 1.1.

In the Phase 2 extension, a repeat scan may be performed as an unscheduled visit at the investigator's discretion to confirm progression 4-6 weeks after the date of the original scan indicating progression. If progression is confirmed the original date of progression will be used for disease assessment.

8.5. Phase 2 and Phase 2 Extension Cardiac Assessment (Screening, Day 84 then every 84 days and EoT visit)

Cardiac assessment to be performed at Screening, on Day 84 then every 84 days and at EoT visit. It will be performed by the study investigator and be based on assessment of medical history, physical examination, 12-lead ECG results and evaluation of left ventricular ejection fraction (LVEF) by echocardiography or MUGA scan.

8.6. Phase 2 and Phase 2 Extension Laboratory Assessments

Hematology and serum chemistry analyses will be performed by an accredited local laboratory. Serum predication markers of tumor progression and intra-tumor T cell and biomarker analysis will be performed by an accredited central laboratory. Humoral and cellular immunological analysis will be performed by an accredited specialist central immunology laboratory.

Unused blood /serum and/or tissue samples collected during the study from patients who have signed an appropriate informed consent form may be stored and used for future research. The coded samples may be stored up to 15 years after the clinical study ends. A patient may contact the investigator to have their unused samples destroyed at any time

during the storage period. Results from the future use studies will not be shared with patients.

1) **Safety Laboratory Assessments (Screening, Baseline, Days 21, 42, 63, 84, 105, 126 then every 42 days and EoT visit)**

Blood samples of approximately 10 mL per visit for the assessment of hematological and serum chemistry parameters will be collected and processed in accordance with local laboratory procedures and reference ranges.

Safety laboratory panels are defined as follows:

Human immunodeficiency virus (HIV 1/2 antibodies), hepatitis B (HBsAg reactive) and hepatitis C (HCV ribonucleic acid [RNA] qualitative) (at screening only).

Hematology: Hematology to include CBC, including RBC count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, and C-reactive protein (CRP).

Serum Chemistry: BUN or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT.

2) **Exploratory Endpoint Laboratory Assessments (Baseline, Days 84 then every 84 days and EoT visit)**

A 1 x 10 mL whole blood sample to assess vaccine-specific cytokine levels and in-vitro inhibition of tumor cell growth will be obtained from each patient at Days 0, 84 then every 84 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination.

3) **Phase 2 and Phase 2 Extension Immunologic Assessments**

   a) **Humoral samples (Baseline, Days 21, 42, 63, 84, 126 then every 42 days and EoT visit**

A 1 x 10 mL whole blood sample for humoral immunity will be obtained from each patient at Days 0, 21, 42, 63, 84, 126 then every 42 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination.

   b) **Cellular samples (Screening [Phase 2 Extension only], Baseline, Days 84 then every 84 days and EoT visit)**

Collection of 40 mL blood sample will be performed for PBMC isolation and analysis of cellular parameters at Days 0, 84 then every 84 days and at EoT visit. When vaccination with IMU-131 occurs, these samples will be taken prior to vaccination.

During the Phase 2 Extension study, a Screening Visit collection of 40 mL blood sample for PBMC isolation and analysis of cellular parameters will be performed after enrolment eligibility including HER2 over-expression is confirmed.

8.7. Phase 2/Phase 2 Extension HER2/neu overexpression (Screening)

Confirmation of HER2/neu overexpression is required for inclusion in this study.

A previous pathology result confirming HER2/neu overexpression is acceptable. If analysis of a tumor biopsy is required for confirmation of HER2/neu overexpression, then this may be achieved via analysis of a fresh or archived tissue sample.

HER2/neu analysis will be conducted at each center's local pathology laboratory by immunohistochemistry (IHC) and fluorescent *in situ* hybridization [FISH], brightfield double *in situ* hybridization [BDISH], or chromogenic *in situ* hybridization [CISH] if IHC result is equivocal.

Using the IHC method an unequivocal result of HER2 overexpression is defined as HER2 +++, an equivocal result is defined as HER2 ++, and a negative result is defined as HER2 +. If equivocal result (IHC HER2 ++) then additional analysis via FISH, BDISH or CISH will be conducted for confirmation of HER2 overexpression. The definition of FISH, BDISH or CISH positivity in gastric or gastro–esophageal junction cancer is a HER2: chromosome 17 ratio of ≥2.0.

8.8. Phase 2/Phase 2 Extension ECOG performance grade (Screening, Baseline, Days 84 then every 84 days and EoT visit)

The ECOG performance grade should be determined using the criteria defined in Appendix 3: ECOG Performance Status Scale.

8.9. Phase 2/Phase 2 Extension Pregnancy Test (at each study visit, excluding post- treatment follow-up visits)

For female patients of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed immediately before administration of each vaccine dose. A negative pregnancy test result is required before the patient may receive the investigational product. If urine pregnancy test is positive, then confirmation of pregnancy will be by local laboratory BHCG blood test. If BHCG blood test is negative, then vaccination schedule may resume.

8.10. Phase 2/Phase 2 Extension Intra-tumor analysis (Screening, Day 84 and post- progression)

A screening visit or archival tumor biopsy sample will be obtained for all patients for intra-tumor analysis (unless HER2 status has been confirmed previously and archival tissue is not available). An optional Day 84 and optional post-progression tumor sample will be requested from patients. These samples will be analyzed for intra-tumor T cells and biochemical markers. The screening visit biopsy sample may also be used to determine HER2/neu overexpression.

8.11. Phase 2/Phase 2 Extension Unscheduled Visit

Unscheduled visits may be conducted at any time during Phase 2 by the investigator if clinically indicated for the care of the patient.

An unscheduled visit may include any of the protocol required assessments listed in Section 8: Phase 2 Assessments. The exact assessments conducted at the unscheduled visit will be specified by the investigator and recorded in the CRF. Additional tests and procedures may be performed at the unscheduled visit for the clinical care of the patient after discussion with, and agreement of, the medical monitor.

8.12. Phase 2 Post-treatment Follow Up (FU) Visit (Every 42 days after EoT visit)

After disease progression, anti-cancer therapy and survival information will be collected every 6 weeks until death, withdrawal or end of trial. Anti-cancer therapy and survival information may be collected more frequently than every 6 weeks for quality control and data cleaning purposes. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 6 weeks until determination of progressive disease.

All patients will be followed for radiographic change until determination of progressive disease and survival information and anti-cancer treatment until death, unless the patient requests to be withdrawn from radiographic change assessment and survival follow-up contact or the trial ends. Requests for withdrawal must be documented in the source documents and signed by the investigator.

Phase 2 extension patients will no longer complete Post-Treatment Follow Up visits.

9. ADVERSE EVENT REPORTING

9.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited with respect to particular AEs.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Imugene Limited or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. AEs will be followed until resolved, stable, or until the subject's last study visit or lost to follow-up. If an AE is not resolved or stabilized at the subject's last visit, it is up to the discretion of the investigator and the Sponsor's medical monitor to determine if further monitoring of the event is warranted.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

9.2. Reporting Period

For AEs/SAEs, the active reporting period to Imugene Limited or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product, including administration during long term maintenance. After informed consent has been obtained but prior to initiation of study drug(s), only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

The cause of death must be reported as an SAE if it occurs at any time after the SAE reporting period and is likely to be related to the investigational product.

9.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death (not due to disease progression);
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Is determined to be an important medical event by the study investigator.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.5.1. Adverse Events of Special Interest

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who

present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X LLN (whichever is smaller).
- **Concurrent with**
    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the lower limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. For oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

9.6. Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

9.7. Adverse Event Severity Assessment

9.7.1. Local (injection site) Adverse Event Intensity:

Intensity of the following local AEs should be assessed as described in the table below adapted from the FDA, Center for Biologics Evaluation and Research (CBER), *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccinxe Clinical Trials* dated September, 2007:

Table 4: Grading of Local Adverse Event Intensity

Local Reaction to Injectable Product	Absent (Grade 0)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Absent	Does not interfere with activity	Repeated use of non- narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Absent	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness *	Absent	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling**	Absent	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

9.7.2. Other Adverse Event Intensity Grading

Patients will be evaluated for safety if they have received any treatment. Adverse events and other symptoms will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events version 4.03 (CTCAE v4.03) in Phase 1b and with version 5.0 (CTCAE v5.0) in Phase 2/Phase 2 Extension.

Table 5: Common Toxicity Criteria for Adverse Events version 4.03 (CTCAE v4.03) and version 5.0 (CTCAE v5.0) Grading

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 or 5.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

9.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 9.12: Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

9.9. Pregnancy

Patients who become pregnant during the study period and up to at least 28 days following chemotherapy or 180 days after the last dose of IMU-131 must not receive additional doses of IMU-131 but may continue other study procedures at the discretion of the investigator.

Patients should be instructed to notify the investigator if it is determined after completion of the study that they or their partner (male patients) became pregnant either during the study or within 28 days following chemotherapy or 180 days after the last dose of IMU-131.

If a pregnancy occurs within 28 days following chemotherapy or 180 days after the last dose of IMU-131, the pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to Imugene Limited after delivery. The mother may freely choose to terminate the pregnancy as her own decision. Neither the Sponsor nor investigators should influence this decision in any way. Similarly, neither the investigators nor Sponsor have the right to intervene or influence

this decision and any ensuing procedures. If this occurs, the termination of pregnancy should be considered an elective surgical procedure and any associated adverse events attributed accordingly.

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

9.10. Withdrawal Due to Adverse Events (See Also Section 6.5: Patient Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 9.12.

9.11. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

9.12. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

9.12.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Imugene Limited, or its delegated representative, is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification must be made immediately to Imugene Limited, or its delegated representative, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Imugene Limited in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Imugene Limited to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Imugene Limited or its designated representative.

9.12.2. Non-Serious Adverse Event Reporting Requirements

All AEs and SAEs that occur after the last informed consent date (i.e. in the case of re-screened patients) will be reported on the AE page(s) of the CRF. It should be noted that an additional form for collection of detailed SAE information will be provided. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

9.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

10. DATA ANALYSIS/STATISTICAL METHODS

10.1. Phase 1b Cohort Review Committee (CRC)

Prior to enrollment of patients into the Phase 1b study, a CRC, comprising relevant site investigators, the Medical Monitor, and Sponsor representatives, will oversee safety, cohort evaluation and dose-escalation for the study. A formal charter which will establish the rules, meeting frequency and scope of responsibilities of the CRC will be established for the conduct of the CRC.

After enrollment in Phase 1b begins the CRC will meet in person or by teleconference as soon as feasible after any of the following occur to determine if the criteria for dose limiting toxicity (DLT) has been met:

- One or more patients experience a serious adverse reaction assessed as related to the vaccine by the investigator
- One or more patients experience anaphylaxis
- Two or more patients in a single dose cohort experience an SAE explained by a diagnosis related to vaccination. (For grading of severity see CTCAE v4.03.)

The CRC will review the safety data and make recommendations on the continuation of the study following the procedures outlined in the CRC charter.

All decisions will be documented in the form of minutes.

10.1.1. Phase 1b Definition of Dose-Limiting Toxicity (DLT)

A dose limiting toxicity (DLT) is defined as a drug-related Grade 3 toxicity that cannot be resolved to a Grade 1 with appropriate therapy within 2 weeks, or a Grade 4 or greater toxicity graded by CTCAE v4.03, related to the IMU-131 vaccine.

10.1.2. Phase 1b Dose Escalation

There will be up to 6 patients in each cohort in Phase 1b. The CRC will review data from one complete cycle of chemotherapy (including 3 doses of IMU-131, on Days 0, 14, and 35) for at least 3 patients in a dose cohort to authorize dose escalation.

A staggered enrollment will be used for patient safety, whereby a dose cohort must be completed and reviewed by the CRC before further recruitment. The decision whether to escalate to the next dose cohort will be made by the CRC when at least 3 patients in the current dose cohort have completed chemotherapy cycle 1 (35 days of the study, including 3 doses of IMU-131 on Days 0,14 and 35).

Phase 1b dose escalation will involve 3 dose levels of IMU-131 with a standard 3+3 scheme for determination of safety prior to dose escalation. Patients will receive 3 doses of IMU-131 (Days 0, 14 and 35) with chemotherapy being initiated 14 days after the first dose of IMU-131 with evaluation occurring after the first 21-day cycle of chemotherapy and before opening the enrollment to the next higher dose cohort.

Dose Escalation Decision Rules

- If 0 out of 3 patients with treatment DLT at a given IMU-131 dose level, enter 3 patients at the next dose level;
- If ≥2 of 3 patients with treatment related DLT at a given dose level, dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose;
- If 1 out of 3 patients with treatment related DLT at a given dose level, enter at least 3 more patients at this dose level. If 0 of these 3 patients experience treatment related DLT, proceed to the next dose level. If 1 or more of this group suffer treatment related DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients may be entered at a dose between the current dose and the next lowest dose level, the exact dose of which will be determined by the CRC.

10.2. Phase 1b Analysis

Demographic data of for the study group will be tabulated.

Safety data:

Listings will be made of the safety data collected at each time point.

[redacted]

Immunogenicity data:

Immunological data for each time point will be analyzed.

[redacted]

Radiographic data:

Radiographic data for each time point will be analyzed.

[redacted]

10.2.1. Phase 1b Efficacy Analysis

The dose effect of IMU-131 will be evaluated in Phase 1b by immunogenicity data: P467-specific antibodies (IgG) and Her-2- specific antibodies (IgG) titers. Additionally, vaccine-specific cytokine responses will be evaluated before and 21 days after the third vaccine dose.

10.2.2. Phase 1b Safety Analysis

The statistical considerations for this study are defined in a detailed Statistical Analysis Plan (SAP). This section focuses on the statistical considerations for the primary objectives. This study and therefore the statistical considerations will be overseen and governed by the CRC and the CRC charter.

The conjecture for Phase 1b is that the cohort receiving the 50 µg dose will have a higher HER2/neu antibody titer than the cohort receiving a lower dose at the assessment time points and that the IMU-131-associated AEs at the 50 µg dose will be acceptable for adoption as recommended phase 2 dose in Phase 2. The study has minimal statistical power for a statistical test ascertaining this conjecture and it will be done descriptively.

10.2.3. Phase 1b Interim Analysis

[redacted]

10.3. Phase 2 Independent Data Monitoring Committee (IDMC)

During Phase 2, an IDMC, comprising independent physicians, an independent statistician, the medical monitor, and Sponsor representatives, will monitor data from the study. The medical monitor and Sponsor representatives will only participate in open sessions at IMDC meetings. The IDMC will be scheduled to meet after 8, 16 and 24 progression events occur and at intervals no less than once per year. Further details of the IDMC meetings and review procedures will be contained in the IDMC charter. A formal charter which will establish the rules, meeting frequency and scope of responsibilities of the IDMC will be established for the conduct of the IDMC.

10.4. Phase 2 Analysis

10.4.1. Phase 2 Analysis Populations

- The Intent-to-Treat (ITT) population: All randomized patients. The primary efficacy analysis will be based on this population. ITT analyses will be conducted on the basis of the randomized treatment.
- The Evaluable Set (EVAL): All randomized patients who receive any amount of study treatment and have at least 1 evaluable post-baseline tumor response. EVAL analyses will be conducted on the basis of the randomized treatment.
- The Full Analysis Set (FAS): All randomized patients who receive any amount of study treatment. FAS analyses will be conducted on the basis of the randomized treatment.
- Safety population: All randomized patients who receive any amount of study treatment. All safety analyses will be based on this population. The safety population will be conducted on the basis of the actual treatment received.
- A Per-Protocol (PP) subset may also be used to analyze select efficacy endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented prior to data base lock.

10.4.2. Phase 2 Efficacy Analysis

[redacted]

Analysis of the primary endpoint, OS, and secondary endpoint, PFS, will be performed using the ITT population. Additional secondary and exploratory analyses of efficacy endpoints will be performed using the ITT, FAS, and/or the EVAL sets. Ancillary analyses of select efficacy endpoints may also be performed using the PP set.

The log-rank method will be used to estimate the secondary efficacy parameter of PFS. Analyses of TTP, DCR, ORR, DOR and CTS will be performed using the same methods as described for PFS. The blinded central review disease response assessments will be used as the primary measure for these analyses, and the Investigator disease response assessments will be used as supportive measures for these analyses.

Patients who are continuing in the study at the time of the primary final analysis will continue to be followed per the schedule of assessments until completion of the study; a supplementary analysis may be produced to reflect any additional data collected after the primary final analysis.

10.4.3. Phase 2 Safety Analysis

All safety analyses will be conducted in the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0, or higher. The severity of AEs will be graded according to NCI CTCAE, version 5.0.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first study drug dose and within 30 days after the last dose date. TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study drug, SAEs, and TEAEs with an outcome of death will be summarized by system organ class, and preferred term for each treatment group. A summary of TEAEs of NCI CTCAE Grade 3 or higher, as well as the most frequent TEAEs (preferred terms), and TEAEs by relationship to study treatment, will be provided. AE incidence rates will also be summarized adjusting for duration of study treatment.

Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to NCI CTCAE 5.0, for applicable tests. Shifts in toxicity grades from baseline grade will be summarized.

Vital signs, ECG, and concomitant medication data will be summarized. Graphical displays will be provided where useful to assist in the interpretation of results.

10.5. Phase 2 Dose Escalation Cohort Review Committee (CRC)

During the Phase 2 dose escalation study, a CRC, comprising relevant site investigators, the Medical Monitor, and Sponsor representatives, will oversee safety, cohort evaluation and dose-escalation for the study. A formal charter which will establish the rules, meeting frequency and scope of responsibilities of the CRC will be established for the conduct of the CRC.

Toxicity data for each cohort will be reviewed prior to dose escalation approval by CRC. Each CRC meeting will be held after each dose cohort has completed Day 35 and prior to initiation of the next dose cohort. The CRC will review the complete, pre-defined safety dataset from each dose cohort and will determine, with advice from the Medical Monitor, the appropriate dose limiting toxicity (DLT) rule (see Section 10.5.1 Definition of Dose-Limiting Toxicity and Section 10.5.2 Dose Escalation Decision Rules, for details) and whether the study will proceed to the next dose cohort. A dose cohort must have completed Day 35 of the study, including 3 doses of IMU-131 and 1 cycle of chemotherapy prior to the CRC meeting and opening of the next higher dose cohort for enrollment. All DLTs will be reviewed by CRC irrespective of whether patients receive 1, 2, or 3 doses of IMU-131 during the DLT assessment period.

The CRC will review all available safety/tolerability and immunogenicity data and make recommendations regarding dose escalation and the continuation of the study following the procedures outlined in the CRC charter.

All decisions will be documented in the form of minutes.

10.5.1. Phase 2 Dose Escalation Definition of Dose-Limiting Toxicity (DLT)

A dose limiting toxicity (DLT) is defined as an IMU-131-related Grade 3 toxicity that cannot be resolved to a Grade 1 with appropriate therapy within 2 weeks, or a Grade 4 or greater toxicity graded by CTCAE v5.0, related to the IMU-131 vaccine.

In addition, after enrollment in Phase 2 dose escalation begins, the CRC will meet by teleconference as soon as feasible after any of the following occur to determine if the criteria for dose limiting toxicity (DLT) has been met:

- One or more patients experience a serious adverse reaction assessed as related to the vaccine by the investigator.
- One or more patients experience anaphylaxis.

10.5.2. Phase 2 Dose Escalation

Between 3 - 6 patients will be enrolled in each Phase 2 dose escalation cohort for safety evaluation by CRC prior to next dose being opened to enrollment. The CRC will review data from one complete cycle of chemotherapy and 3 doses of IMU-131, for at least 3 patients in a dose cohort to authorize dose escalation. The DLT window is 35 days.

Dose escalation in Phase 2 will start at 100µg IMU-131, within a standard 3 + 3 scheme for determination of safety prior to opening enrollment to the 200µg IMU-131 dose cohort. A dose cohort must be reviewed by CRC for DLTs according to dose escalation decision rules before opening the next dosed cohort.

Either the 100µg or 200µg dose escalation cohort may be expanded up to 10 patients after CRC clearance of the 35-day DLT period.

Phase 2 Dose Escalation Decision Rules:

- If 0 out of 3 patients with treatment DLT at a given IMU-131 dose level, enter 3 patients at the next dose level;
- If ≥2 of 3 patients with treatment related DLT at a given dose level, dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose;
- If 1 out of 3 patients with treatment related DLT at a given dose level, enter at least 3 more patients at this dose level. If 0 of these 3 patients experience treatment related DLT, proceed to the next dose level. If 1 or more of this group suffer treatment related DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients may be entered at a dose between the current dose and the next lowest dose level, the exact dose of which will be determined by the CRC.

10.6. Phase 2 Extension Analysis

Dose escalation cohorts will be analyzed and reported when all patients have completed Day 42 RECIST assessment or End of Trial.

Demographic data for the study group will be tabulated.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0, or higher. The severity of AEs will be graded according to NCI CTCAE, version 5.0.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first study drug dose and within 30 days after the last dose date. TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study drug, SAEs, and TEAEs with an outcome of death will be summarized by system organ class, and preferred term for each treatment group. A summary of TEAEs of NCI CTCAE Grade 3 or higher, as well as the most frequent TEAEs (preferred terms), and TEAEs by relationship to study treatment, will be provided. AE incidence rates will also be summarized adjusting for duration of study treatment.

Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to NCI CTCAE 5.0, for applicable tests. Shifts in toxicity grades from baseline grade will be summarized.

Vital signs, ECG, and concomitant medication data will be summarized. Graphical displays will be provided where useful to assist in the interpretation of results.

Immunogenicity data:

Immunological data for each time point will be analyzed.

[redacted]

Radiographic data:

Radiographic data for each time point will be analyzed.

[redacted]

Survival data:

Overall survival data for each patient will be analyzed.

[redacted]

10.6.1. Phase 2 Dose Escalation Safety Analysis

The statistical considerations for this study are defined in a detailed Statistical Analysis Plan (SAP). This section focuses on the statistical considerations for the primary objectives. The Phase 2 dose escalation study, and therefore the statistical considerations, will be overseen and governed by the CRC and the CRC charter.

[redacted]

10.6.2. Phase 2 Dose Escalation Interim Analysis

No formal interim analysis of the Phase 2 dose escalation study is planned. Analysis will be conducted separately for each dose cohort after all patients in each dose escalation and expansion cohort have completed Day 42. [redacted]

10.6.3. Phase 2/Phase 2 Extension General Considerations

Summaries will be performed by treatment and overall. [redacted]

[redacted]

[redacted]

10.7. Sample Size Determination

10.7.1. Phase 1b Sample Size Determination

[redacted]

[redacted]

10.7.2. Phase 2 Sample Size Determination

[redacted]

PFS will be assessed as a secondary outcome with an analysis following 24 evaluable progression events coded using RESIST 1.1 with patients not having a progression being censored at the time of last evaluation for progression or counted as a progression event if death is within 42 days of last evaluation for progression.

Assumptions of accrual time, loss to follow-up, and pooled event rate (both arms combined) used in the sample size calculations may be monitored. The number of patients enrolled, and duration of enrolment and follow-up may be adjusted to achieve the planned number of events at the time of the final analysis of the primary endpoint.

10.7.3. Phase 2 Extension Sample Size Determination

Phase 2 dose escalation will enroll up to 20 patients. No formal statistical calculation of sample size will be used for the Phase 2 dose escalation. The sample size is empirical and based on a standard 3+3 dose escalation design with expansion of up to 10 patients per cohort.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Imugene Limited and should not be made available in any form to third parties, except for authorized representatives of Imugene Limited or appropriate regulatory authorities, without written permission from Imugene Limited.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

11.2. Record Retention

Essential documents such as protocols, amendments, IRB/IEC approvals, signed ICFs, source documents, CRFs, drug accountability records should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, if required by the applicable

regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator or Sub-Investigator and/or institution as to when these documents no longer need to be retained.

The investigator must obtain Imugene Limited's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Imugene Limited, or its agent.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Imugene Limited in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996, 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Imugene Limited, or its delegate, in order to de-identify the trial patient. In case of data transfer, Imugene Limited and its agents will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Imugene Limited, or its agent, before use.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Imugene Limited should be informed immediately.

In addition, the investigator will inform Imugene Limited immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. STUDY CONDUCT CONSIDERATIONS

13.1. Protocol and Investigator's Brochure (IB)

All study personal must be familiar with the protocol to be able to conduct the study in the manner specified.

Imugene Limited has supplied the investigator with an Investigator's Brochure (IB), which describes the vaccine being tested and its known adverse effects. The investigator must be familiar with this document before the study commences. Imugene Limited will provide additional information requested by the investigator before commencing the study or during its conduct.

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Imugene Limited. The protocol amendment must be signed by the investigator and approved by the IRB or IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agencies having jurisdiction over the conduct of the study.

13.2. Confidentiality

Either prior to or during the course of the study, Imugene Limited or their representatives will provide the principal investigator and persons delegated by him/her with confidential information, for example, but not limited to, the protocol and the IB. The information may

not be disclosed to anyone else without prior approval from Imugene Limited in writing. This obligation of confidentiality shall survive the completion or early termination of the study.

13.3. Documentation and Material Supplies

All supplies provided to the investigators for the purpose of carrying out the study are supplied only for the purpose of the study and must not be used for any other purpose. The principal investigator or (a) person(s) delegated by the principal investigator is/are responsible for the security and accountability of all supplies. All such supplies, if not used during the course of the study and not forming a part of the documentation required to be retained by the investigator, must be returned to Imugene Limited at the conclusion of the study.

13.4. Monitoring

The study will be monitored by a CRO. Its representatives will be allowed access to all information resulting from this study and Imugene Limited will have an unrestricted right to use such information. The study monitor will have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The patients' confidentiality will be respected as required by local law.

13.5. Quality Assurance Audit

This study may be audited by Imugene Limited or its designee to document the authenticity of recorded data and protocol adherence. Patients participating in the study should be informed that their records might be reviewed for this purpose, and also by government health authorities. The patients' confidentiality will be respected as required by local law.

13.6. Compensation for Medicine-induced Injury

According to local regulations Imugene Limited will provide insurance coverage to all patients during study period. Imugene Limited assumes liability for and will indemnify all injuries that occur to patients whenever a causal relationship can be established between the event and the clinical trial procedure or the trial substance under study if the following can be demonstrated:

- The event resulted from a trial substance, provided that the substance was administered according to the current protocol and manufacturer's instructions.
- The event occurred as a consequence of diagnostic procedures performed according to the trial protocol.
- The event resulted from therapeutic or diagnostic measures legitimately required as a consequence of unexpected events caused by the trial substance, by comparative medication, or by diagnostic procedures called for by the trial protocol.

Imugene Limited is not liable for events that occur solely as a consequence of the underlying illness of the patient, or for events resulting from diagnostic or therapeutic measures not specifically required by the protocol, or for events resulting from negligence

(including failure to act according to accepted medical practice, or to comply strictly with the protocol or the terms of this Agreement) of the investigator or any other involved and/or related clinical staff and facilities.

This indemnity provided by Imugene Limited shall further apply as follows:

Imugene Limited is to be informed as soon as possible of any complaint, action or suit of proceeding giving rise to the right of indemnification, and the investigator agrees to co-operate fully with Imugene Limited in the defense or disposition of all such cases.

Imugene Limited will be permitted, at its costs and discretion, to handle and control the defense or disposition of all such cases.

No case will be settled without the prior written consent of Imugene Limited.

14. DEFINITION OF END OF TRIAL

End of trial is defined as 28 days post the last patient completing the end of treatment visit.

15. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Imugene. In addition, Imugene retains the right to discontinue development of IMU-131 at any time.

If a study is prematurely terminated or discontinued, Imugene will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 7 days. As directed by Imugene, all study materials must be collected and all CRFs completed to the greatest extent possible.

16. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

In accordance with standard editorial and ethical practice, Imugene Limited will support publication of multicenter trials only in their entirety and not as individual center data except for data on substudies.

The following rules will apply for determining authorship:

Authorship credit will be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e. substantial contribution to the following criteria:

i) Conception and design or analysis and interpretation;
ii) Drafting article or critically revising it for intellectual content;
iii) Final approval of the version to be published;

Additional criteria for authorship include:

iv) Contributors who register 20% or more of the evaluable cases on the study;
v) Significant contribution to the Cohort Review Committee.

In an appropriate footnote, or at the end of the article, the following statement will be made:

> "Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

Investigator agrees to submit all manuscripts or abstracts to Imugene Limited prior to submission. This allows Imugene Limited to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the authors of the manuscript. Investigator will collaborate with the study statistician for preparation of trial data analyses intended to be used in the publication(s) of the study.

Any formal publication of the study in which input of Imugene Limited personnel exceeded that of conventional monitoring will be considered as a joint publication by Investigator and Imugene Limited.

Moreover, the following points need to be considered:

- Without Investigator's prior written consent, Imugene Limited may not make reference, either directly or indirectly, in a commercial publication, to Investigator's name or institution, or any of its employees in which Investigator performed the present trials, connected with the research and its results.
- Imugene Limited may not use Investigator's name or the name of the [redacted] or its employees connected to the research or to the institution in which Investigator performed the present trial in its commercial publications as recommendation of quality and/or of the finished product and/or of the drug and the efficacy of its use.
- Should Imugene Limited decide to publish the research results, it must publish them in their entirety and must not quote anything out of context.

Nothing in the aforementioned limitations in clauses will prevent Imugene Limited from quoting from articles, provided that the scientific source of data (scientific conventions, scientific newspapers) is mentioned.

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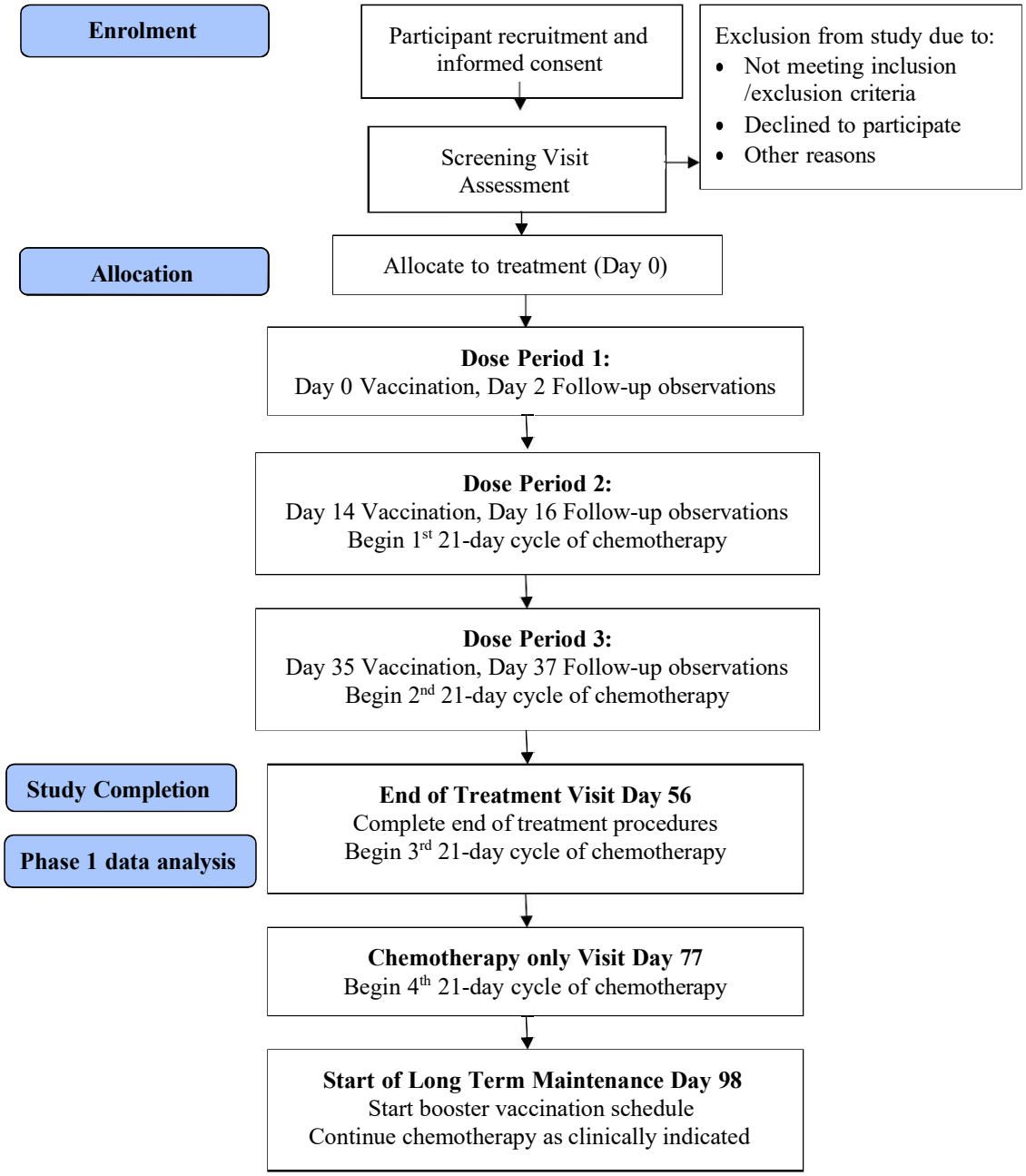
APPENDIX 1: FLOW DIAGRAM OF PHASE 1B



APPENDIX 2: VACCINE – MONTANIDE EMULSION PREPARATION INSTRUCTIONS

The vaccine – montanide emulsion preparation instructions can be found in the pharmacy manual.

APPENDIX 3: ECOG PERFORMANCE GRADE SCALE

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX 4: THAILAND SPECIFIC PROTOCOL ADDENDA #1

Investigational Product: IMU-131
Protocol Identifier: IMU.ACS.001
Original Protocol Version: 6 April 2016
Addenda Protocol Version: Thailand Specific Protocol Addenda #1_2 Feb 2017

A PHASE 1B/2 OPEN-LABEL STUDY OF IMU-131 HER2/NEU PEPTIDE VACCINE PLUS CISPLATIN AND EITHER 5-FLUOROURACIL OR CAPECITABINE CHEMOTHERAPY IN PATIENTS WITH HER2/NEU OVEREXPRESSING METASTATIC OR ADVANCED ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

Compound: IMU-131

Compound Name (if applicable): HER-Vaxx

Protocol Number: IMU.ACS.001
Thailand Specific Protocol Addenda # 1_2 Feb 2017

Sponsor: Imugene Limited
Suite 1, 1233 High Street
Armadale, VIC 3143
Tel: +61 3 9824 5254
+61 458 040 433

Document History

Document	Version Date	Summary of Changes
Original protocol	6 April 2016	N/A
Thailand specific protocol addenda #1	2 February 2017	Additional Exclusion Criteria to exclude patients with diphtheria toxoid hypersensitivity

This Thailand Specific Protocol Addenda #1_2 Feb 2017 adds an additional exclusion criteria to the 14 exclusion criteria present in Section 4.2 of the original protocol dated 6 April 2016, and applies to all Thailand study sites conducting Protocol IMU.ACS.001.

This additional exclusion criteria will be incorporated into the full study protocol at the next protocol amendment.

4.2 Exclusion Criteria

In addition to the 14 exclusion criteria present in the original protocol dated 6 April 2016, the following exclusion criteria has been added to the study protocol:

15. Patients with a known diphtheria toxoid hypersensitivity will not be included in the study.

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APPENDIX 5: TAIWAN SPECIFIC PROTOCOL ADDENDA #1

Investigational Product: IMU-131
Protocol Identifier: IMU.ACS.001
Original Protocol Version: 6 April 2016
Addenda Protocol Version: Taiwan Specific Protocol Addenda #1_13 Mar 2017

A PHASE 1B/2 OPEN-LABEL STUDY OF IMU-131 HER2/NEU PEPTIDE VACCINE PLUS CISPLATIN AND EITHER 5-FLUOROURACIL OR CAPECITABINE CHEMOTHERAPY IN PATIENTS WITH HER2/NEU OVEREXPRESSING METASTATIC OR ADVANCED ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

Compound: IMU-131

Compound Name (if applicable): HER-Vaxx

Protocol Number: IMU.ACS.001
Taiwan Specific Protocol Addenda # 1_13 Mar 2017

Sponsor: Imugene Limited
Suite 1, 1233 High Street
Armadale, VIC 3143
Tel: +61 3 9824 5254
+61 458 040 433

Document History

Document	Version Date	Summary of Changes
Original protocol	6 April 2016	N/A
Taiwan specific protocol addenda #1	13 March 2017	To confirm the sequential enrolment of Taiwanese patients - at least 14 days apart in the first dose cohort To increase the observation time for the first Taiwan patient dosed in the study to 6 hours post first injection

This Taiwan Specific Protocol Addenda #1_13 March 2017 adds additional information to the original protocol dated 6 April 2016 per the requirements of Taiwan Food And Drug Administration, and applies to all Taiwan study sites conducting Protocol IMU.ACS.001.

This additional information will be incorporated into the full study protocol at the next protocol amendment.

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Investigational Product: IMU-131
Protocol Identifier: IMU.ACS.001
Original Protocol Version: 6 April 2016
Addenda Protocol Version: Taiwan Specific Protocol Addenda #1_13 Mar 2017

The following contents are added to the study protocol dated 6 April 2016:

9.1.2. Dose Escalation within Phase 1

Sequential enrollment will be applied specifically in the first dose cohort in Taiwan. In the first dose cohort of phase 1b study, the first dosing on each Taiwanese patient should be at least 14 days apart.

6.2.2. Dose Period 1 (Day 0 and Day 2)

On Day 0/Baseline, for safety observation, Taiwanese patients are required to stay in the institution for at least 6 hours after administration of IMU-131.

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APPENDIX 6: FLOW DIAGRAM OF PHASE 2