NCT03009058

PROTOCOL SYNOPSIS

IMM-101-011

A Novel Phase I/IIa Open-label Study of IMM-101 in Combination with Selected Standard of Care (SOC) Regimens in Patients with Metastatic Cancer or Unresectable Cancer at Study Entry.

CONFIDENTIAL
CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Novel Phase I/IIa Open-label Study of IMM-101 in Combination with Selected Standard of Care (SOC) Regimens in Patients with Metastatic Cancer or Unresectable Cancer at Study Entry.
SHORT TITLE:	MODULATE
PROTOCOL NUMBER:	IMM-101-011
EUDRACT NUMBER:	2016-001459-28
DRUG:	IMM-101
SPONSOR:	Immodulon Therapeutics Limited 6-9 Stockley Park Uxbridge UB11 1FW United Kingdom
CHIEF INVESTIGATOR:	REDACTED GI & Lymphoma Department Royal Marsden Hospital Foundation Trust Fulham Road London SW3 6JJ

VERSION TABLE

Version 4.00 FINAL HIGHLIGHT protocol	25 October 2016
Version 3.00 FINAL protocol	09 September 2016
Version 2.00 FINAL protocol (not submitted)	12 August 2016
Version 1.00 FINAL protocol (not submitted)	01 August 2016

STATEMENT OF CONFIDENTIALITY

This protocol report may not be reproduced or communicated to a third party without the written permission of Immodulon Therapeutics Ltd.

SIGNATURE PAGE

This study protocol was subjected to critical review. The information it contains is consistent with the current risk/benefit evaluation of the test preparation as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

This protocol is approved by:

REDACTED Chief Investigator Royal Marsden Hospital, London	Signature	Date
REDACTED Medical Monitor Immodulon Therapeutics Ltd	Signature	Date
REDACTED Statistical Advisor Immodulon Therapeutics Ltd	Signature	Date

CONTACT DETAILS

SPONSOR:	Immodulon Therapeutics Ltd. 6-9 The Square, Stockley Park, Uxbridge, UB11 1FW United Kingdom (UK) Tel: +44 (0) 208 929 9282 Fax: +44 (0) 208 929 9283
MEDICAL MONITOR	REDACTED Immodulon Therapeutics Ltd. 6-9 The Square, Stockley Park, Uxbridge, UB11 1FW UK Tel: +44 (0) 208 929 9282 Mobile: +44 (0) 7762 783 689 Email: el@immodulon.com
CHIEF INVESTIGATOR:	REDACTED Professor/Consultant Medical Oncologist GI & Lymphoma Department, Royal Marsden Hospital Foundation Trust, Fulham Road, London SW3 6JJ Tel.: 020 7808 2123 Email: ProfDavid.Cunningham@rmh.nhs.uk
SERIOUS ADVERSE EVENT CONTACT DETAILS:	Emas Pharma 63-65 Knowl Piece, Wilbury Way, Hitchin, Hertfordshire, SG4 0TY, UK. Tel.: +44 (0)1462 424416 Fax: +44 (0)1462 600456 Email: Drug.Safety@emaspharma.com

This Protocol has been written in accordance with current ICH-GCP guidelines.

1. PROTOCOL SYNOPSIS

Title	A Novel Phase I/IIa Open-label Study of IMM-101 in Combination with Selected Standard of Care (SOC) Regimens in Patients with Metastatic Cancer or Unresectable Cancer at Study Entry.
Short Title	MODULATE
Protocol Number	IMM-101-011
EudraCT Number	2016-001459-28
Investigational Product	IMM-101: A suspension, in borate-buffered saline, of heat-killed whole cell *Mycobacterium obuense* (National Collection of Type Cultures [NCTC] 13365) for intradermal injection.
Chief Investigator	REDACTED GI & Lymphoma Department Royal Marsden Hospital Foundation Trust Fulham Road London, SW3 6JJ
Number of Sites and Countries	Up to 10 sites globally.
Phase	Phase I/IIa.
Indication	Patients with metastatic or unresectable cancer considered for a new line of recognised SOC (first, second and third line and beyond) as defined in this protocol. Patients must have a life expectancy of at least 3 months to ensure adequate time for a response to treatment to be detected.
Study Rationale	No safety concerns were evident in the previous Phase I and Phase II studies which have been performed with IMM-101, however there is limited safety and exposure data available. In addition, in a 110 patient Phase II clinical study in advanced pancreatic cancer, IMM-101, administered with gemcitabine, has been demonstrated to result in clinically relevant survival benefits and improvements in progression free survival (PFS). This was achieved without significant additional toxicity. Therefore, the Sponsor considers it appropriate to perform safety analyses in cancer patients in combination with a variety of selected SOC regimens. Activity data will also be analysed in this study. Selection of SOC for this protocol has been made based on scientific rationale and recognised regimens for the treatment of unresectable or metastatic cancers.
Study Design	During this open-label study, patients who provide informed consent, will participate in a Screening period of up to a maximum of 28 days to establish eligibility before enrolment. Once eligibility is confirmed, patients will enter the Treatment Phase of the study and follow the Study Schedule of Assessments (**Error! Reference source not found.**). Patients will receive IMM-101 in conjunction with recognised SOC for metastatic or unresectable cancer for the patient's specific tumour type. The recognised SOC regimens and the cancer types that will enable a patient to be entered into the study are as follows: **Synopsis Table 1: Planned Combinations of Standard of Care and Type of Cancer for the IMM-101-011 Study**

Treatment/disease	Pancreatic	Colorectal	Cholangio	Lung	Melanoma	Breast	Sarcoma
Gemcitabine (GEM)	X		X	X	X	X	X
Gemcitabine + nab-paclitaxel	X			X		X	
Gemcitabine + capecitabine	X						
FOLFIRINOX	X						
FOLFOX		X					
FOLFIRI + cetuximab		X					
Anti-PD1 (pembrolizumab, nivolumab)				X	X		
Anti-CTLA-4 (ipilimumab)					X		
Low-dose cyclophosphamide	All patients with solid malignancies: Low-dose cyclophosphamide (300mg/m^2) will be given by infusion approximately 4 hours prior to IMM-101 on days 0, 28, and 56						

anti-CTLA-4: anti-cytotoxic T-lymphocyte-associated protein-4; anti-PD1: anti-programmed cell death-1 receptor; FOLFIRI: **FOL**inic acid, **F**luorouracil and **IRIn**otecan; FOLFIRINOX: **FOL**inic acid, **F**luorouracil, **IRIN**otecan and **OX**aliplatin; FOLFOX: **FOL**inic acid, **F**luorouracil and **OX**aliplatin.

Patients will only be considered for entry into the study when they are commencing a new line of SOC, they cannot enter the study mid-way through their current line of therapy.

Following entry to the study, upon progression to immune related response criteria (irRC) or intolerability and toxicity to the selected SOC regimen, the treating physician can continue systemic treatment with an established line of treatment chemotherapy (in the respective disease group) in addition to IMM-101. An exception would be where reasons for discontinuation were due to IMM-101 toxicity. Changing from a selected SOC regimen to treatment with either an anti-PD1 or an anti-CTLA-4 agent will not be allowed on study..

Standard IMM-101 Dosing Regimen: All patients (except for those detailed below) will receive IMM-101 every 2 weeks for the first 3 doses, followed by a rest period of 4 weeks, then patients will receive IMM-101 every 2 weeks for the next 3 doses, and thereafter every 4 weeks (or as close to this interval as permitted due to practical or logistical considerations) for up to 28 weeks and will follow the Study Schedule of Assessments (**Error! Reference source not found.**).

Reduced Intensity IMM-101 Dosing Regimen: In order to ensure that there are no increased immune-related adverse events (AEs), the first 3 patients entering the anti-PD1 (pembrolizumab or nivolumab) cohort **and** the first 3 patients entering the anti-CTLA-4 (ipilimumab) cohort will receive IMM-101 at an increased dosing interval of every 4 weeks. In the

	absence of safety concerns for these patients after 3 doses of IMM-101, and following a robust safety review, all subsequent patients recruited to these treatment cohorts will switch to the standard, more intensive (2-weekly induction dosing) IMM-101 dosing regimen. At Week 32, if the Investigator considers it in the patients' best interest patients will progress to the Maintenance Phase of the study and will continue to be dosed every 4 weeks (or as close to this interval as permitted due to practical or logistical considerations). Patients will be followed up for assessment of safety, response to treatment, survival, and immunological markers for up to 4.5 years and will follow the Study Schedule of Assessments (**Error! Reference source not found.**). Patients withdrawing from the study during either the Treatment or Maintenance Phases should attend an end of study (EOS) visit within 28±7 days after the final dose of IMM-101. Prospective cohorts for safety and activity are defined in the statistical methodology. Depending on the outcome of this study, where there is evidence of activity of IMM-101 in any given disease, with a given SOC, a series of separate, randomised, follow-up, adaptive, Phase II/III studies will compare clinical outcomes, such as response and PFS, between IMM-101+SOC versus SOC alone. These Phase adaptive II/III studies will be statistically designed for the purposes of decision-making in terms of the requirement for further large-scale confirmatory randomised studies.
Objectives	The primary objective of the study is to provide safety data for IMM-101 in combination with a number of selected SOC regimens. The secondary objectives of the study are to provide • Safety and tolerability data for extended admininstration (beyond 28 weeks) of IMM-101 in combination with a number of selected SOC regimens (• Synopsis Table **1**). • Establish safety data for the combination of IMM 101 with anti PD1 (pembrolizumab, nivolumab) and with anti-CTLA 4 (ipilimumab). • Preliminary data regarding the activity of IMM-101 (in terms of response to treatment) in combination with recognised SOC in a number of different tumour types. • Disease outcome data. • Monitoring of selected markers of tumour burden and immunological status in patients taking IMM-101.
Study Duration	The study will continue until all patients have either withdrawn from the study or died. It is anticipated that the study will continue for approximately 5 years to facilitate adequate follow up of long-term survivors. The written consent document will include permission for the Investigator or designee to contact the patient's general practitioner (GP) for continued collection of survival data in the event of withdrawal and the continued collection and evaluation of immune response for withdrawn patients with exceptional responses.

Principal Selection Criteria	Patients are eligible to be included in the study if they: 1. Have metastatic or unresectable cancer and are considered by their physician to be indicated for a new line of SOC, as listed 2. Are ineligible for a disease-specific clinical study with IMM-101 3. Have an estimated life expectancy greater than 3 months (from Day 0) 4. Give signed informed consent for participation in the study 5. Have an Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) Performance Status of ≤2 at Day 0. Two observers will be required to assess performance status. If there is any discrepancy between the two scores, the highest (worst) assessment will be used 6. Have adequate bone marrow, hepatic and renal function including the following: a. Haemoglobin (Hb) ≥9.0g/dL, absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥75 x 10^9/L b. Total bilirubin ≤1.5 x upper limit of normal (ULN), excluding cases where elevated bilirubin can be attributed to Gilbert's Syndrome c. Aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT; serum glutamate pyruvate transaminase [SGPT]) ≤5 x ULN d. Creatinine ≤1.5 x ULN e. Serum albumin >28g/L f. International normalised ratio (INR) <1.5 or a prothrombin time/partial thromboplastin time (Pt/PTT) within normal limits g. C-reactive protein (CRP) <20 mg/L for patients with solid tumours 7. Are aged ≥18 years. Patients will be ineligible if one or more of the following statements are applicable: 1. Patient has previously received treatment with IMM-101 2. Patient is currently part way through a course of chemotherapy or immunotherapy 3. Patient is receiving concomitant treatment with another investigational product 4. Patient has received an investigational drug within the 4 weeks prior to IMM-101 administration 5. Patient has significant cardiovascular disease as defined by: a. History of congestive heart failure requiring therapy b. History of unstable angina pectoris or myocardial infarction up to 6 months prior to study entry c. Presence of valvular heart disease d. Presence of a ventricular or supra-ventricular arrhythmia requiring ongoing treatment

	e. Left ventricular ejection fraction (LVEF) <50% (or less than the institutional norm) 6. Patient has any previous or concurrent malignancy. Patients will not be excluded if they have adequately treated carcinoma *in situ* of the cervix, basal cell carcinoma of the skin and/or non-melanoma skin cancer, or if previous malignancy was more than 5 years prior to Screening and there are no signs of recurrence 7. Patient has co-existing active infection or medical condition which, in the Investigator's judgement, will substantially increase the risk associated with the patient's participation in the study 8. Patient has uncontrolled hypercalcaemia (National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events [CTCAE] v4.0[1] >Grade 1) 9. Patient has previously experienced an allergic reaction to any mycobacterial product. 10. The patient has a history of non-infectious pneumonitis that required steroids or current pneumonitis 11. Received live vaccine within 30 days of planned start of study medication 12. Patient is pregnant or a breast-feeding woman. Female patients with reproductive potential must have a negative serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) within 72 hours prior to start of the study. Both women and men must agree to use a medically acceptable, effective method of contraception throughout the treatment period and for at least 6 months after discontinuation of treatment. In addition, women treated with low dose cyclophosphamide must be instructed to use adequate, effective contraception whilst taking part in the study and for at least 12months after discontinuation of treatment. Acceptable, effective methods of contraception include intrauterine device (IUD), intrauterine hormone releasing system (IUS), oral contraceptive (progestogen-only oral contraception that does not inhibit ovulation is not an acceptable method), bilateral tubal occlusion, vasectomised partner, and subdermal implant 13. Patient has used depot corticosteroids in the 6 weeks before initiation of Screening (signing of the informed consent form [ICF]) 14. Patient has had chronic use of systemic corticosteroids (>10 mg per day of prednisolone or equivalent for a period of 2 weeks or more) and/or immunosuppressant drugs (such as azathioprine, tacrolimus, cyclosporin) within the 2-week period before the first administration of IMM-101 15. Patient has received a blood transfusion within 4 weeks prior to Screening 16. In the opinion of the Investigator, the patient is unable or unwilling to comply with the protocol.

Investigational Product Formulation	IMM-101 is a suspension of heat-killed whole cell *M. obuense* (NCTC 13365) in borate-buffered saline.
Dosage	A single 0.1 mL intradermal injection of IMM-101 (10 mg/mL).
Administration	**Standard IMM-101 Dosing Regimen:** The treatment regimen with IMM-101 will be one dose given every 2 weeks for the first 3 doses followed by a rest period of 4 weeks, then one dose every 2 weeks for the next 3 doses. This is followed by a dose every 4 weeks thereafter (or as close to this interval as permitted due to practical or logistical considerations). **Reduced Intensity IMM-101 Dosing Regimen:** The first 3 patients enrolled in the anti-PD1 cohort and the first 3 patients enrolled in the anti-CTLA-4 cohort will be dosed at 1 mg every 4 weeks (i.e. increase in dosing interval) throughout. In the absence of safety signals, subsequent patients recruited to these treatment cohorts will be dosed with the standard IMM-101 dose regimen described above. During the Treatment Phase of the study (Doses 1 to 3 and Doses 4 to 6), at the discretion of the Investigator, the dose interval may be modified provided the minimum period between doses is at least 11 days (14±3 days). However, in the event that this minimum dosing interval cannot be maintained, at the discretion of the Investigator, a half dose of IMM-101 (0.5 mg/0.05 mL intradermal injection) should be given and at no point in the study should any doses of IMM-101 be administered at less than a 7-day interval. Where this reduced dosing interval is being used the 4-week interval between Dose 3 and Dose 4 and between Dose 6 and Dose 7 should still be maintained. In the event of an injection site reaction of ≥Grade 3 (severe) as measured by the NCI CTCAE v4.0[1], at the discretion of the Investigator, patients may be administered a half dose of IMM-101 (i.e., a single 0.05 mL intradermal injection of IMM-101). During the Maintenance Phase of the study, in the event of an injection site reaction ≥Grade 3 (severe) as measured by the NCI CTCAE v4.0[1], or at the discretion of the Investigator, patients may be administered a half dose of IMM-101 (0.5 mg/0.05 mL) or the dosing interval may be increased or both. If the dosing interval is increased, the patient should attend the study site for safety assessments at least every 14 weeks. IMM-101 is given via intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose. Additional safety measures have to be considered for patients in thecheckpoint inhibitor (CPI) cohort due to the safety profile of the CPI. These safety measures are presented in Synopsis Table 2:

Synopsis Table 2: Additional Safety Measures for Patients in the IMM-101+CPI Cohort

Adverse reaction	Severity of reaction	Action to be taken
Any immune-mediated adverse reactions	Severe	Permanently discontinue IMM-101 and CPI.
	Moderate	Withhold IMM-101 and CPI until condition returns to baseline, improves to mild severity, or there is complete resolution, and patient is receiving less than 7.5 mg prednisone or equivalent per day.
	Persistent, or recurring	Withhold IMM-101+CPI until resolution
Immune-mediated hepatitis	All	Evaluate liver function tests before each dose of ipilimumab, pembrolizumab or nivolumab
Immune-mediated endocrinopathies	All	Monitor clinical chemistries, ACTH level, and thyroid function tests prior to each CPI dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Initiate hormone replacement therapy as needed. Withhold IMM-101 + CPI until resolution
Type 1 diabetes mellitus	All	Monitor for hyperglycemia
	Severe hyperglycemia	Withhold IMM-101+CPI until resolution
Immune-mediated pneumonitis	Moderate	Withhold IMM-101+CPI until resolution
	Severe, life-threatening or recurrent moderate pneumonitis	Permanently discontinue IMM-101+CPI
Immune-mediated colitis	Moderate or severe	Withhold IMM-101+CPI until resolution
	Life-threatening	Permanently discontinue IMM-101+CPI
Immune-mediated nephritis	All	Monitor for changes in renal function
	Moderate	Withhold IMM-101+CPI until resolution
	Severe or life-threatening nephritis	Permanently discontinue IMM-101+CPI

Prohibited Medication	Chronically administered systemic or depot corticosteroids or immunosuppressant drugs (such as azathioprine, tacrolimus, cyclosporin) should not be administered to patients in this study.
Visit Schedule	The study will consist of three phases – Screening Phase, Treatment Phase and Maintenance Phase. Details of the Study Schedule are shown in **Error! Reference source not found.** and **Error! Reference source not found.**.

Safety and Tolerability Endpoints:	• AEs • Laboratory abnormalities • Local injection site reactions.
Activity Endpoints:	• Response to treatment, (defined as immune-related Stable Disease [irSD], immune-related Partial Response [irPR] and immune-related Complete Response [irCR]) as assessed by the Investigator • Overall survival (OS) • Immunological markers (Serum: micro ribonucleic acid [miRNA] panel, circulating metabolites. FACS: immune cell quantifications: TruCulture: cytokines, chemokines, immune mediators, functional immune cell assays, tumour markers) • Additional evaluations may be considered as driven by the evolving understanding of the mechanism of action, technical feasibility, and any other clinical or immunological information that may become available. **Assessment of immune-related Response Criteria (irRC):** • irCR is the disappearance of all lesions, measured or unmeasured, and no new lesions • irPR is a ≥50% drop in tumour burden from baseline as defined by the irRC • Immune-related Progressive Disease (irPD) is ≥25% increase in tumour burden from the lowest level recorded • Everything else is considered irSD. The justification for using this measure for this study is that even if tumour burden is rising, the immune system is likely to 'kick in' some months after first dosing and lead to an eventual decline in tumour burden for many patients.[2] The 25% threshold allows this apparent delay to be accounted for. In the irRC, tumour burden is measured by combining 'index' lesions with new lesions. Ordinarily tumour burden would be measured simply with a limited number of 'index' lesions (that is, the largest identifiable lesions) at baseline, with new lesions identified at subsequent timepoints counting as 'Progressive Disease'. In the irRC, by contrast, new lesions are simply a change in tumour burden. The irRC retains the bidirectional measurement of lesions that had originally been laid down in the WHO Criteria. Upon upon progression to irRC or intolerability and toxicity to the selected SOC regimen, the treating physician can continue systemic treatment with an established line of treatment chemotherapy (in the respective disease group) in addition to IMM-101. An exception would be where reasons for discontinuation were due to IMM-101 toxicity. Changing from a selected SOC regimen to treatment with either an anti-PD1 or an anti-CTLA-4 agent will not be allowed on study.
Statistical Methods/Sample Size	The activity of IMM-101 will be assessed under each SOC by tumour type as follows: • For each SOC/tumour type 10 patients will be treated. After the tenth patient has reached the Week 28 visit, futility will be assessed in terms of calculating the posterior probability that response rate of SOC in combination with IMM-101 is at least that expected for SOC alone; if

	this posterior probability is <33%, then IMM-101 will be considered as futile when administered in combination with the given SOC. • Since the first 10 patients treated for a given SOC/tumour type may include 3 (or possibly more) patients receiving reduced exposure to IMM-101, to avoid an inflation of the type II error, the assessment of futility may wait until 10 subjects have been treated with the standard, more intensive (2-weekly induction dosing) IMM-101 dosing regimen. The need to wait will be judged on a cohort by cohort basis as the trial unfolds. • If IMM-101 is found to not be futile, then a further 10 patients will be recruited and efficacy assessed on the total of 20 patients where efficacy is defined as a posterior probability of ≥80% that the response rate for IMM-101 administered in combination with SOC is higher than that expected with SOC alone. Safety and activity data arising from this study will be summarised and displayed by SOC. Safety data will be listed. Exact binomial confidence intervals (CIs) will be calculated for the observed response rate by tumour type within SOC grouping. Duration of response and survival will be summarised by Kaplan-Meier (KM) methods, again by tumour type and within each SOC grouping. Based on selected SOCs and tumour types, it is envisaged that approximately 300 patients will be recruited into this open-label study. CPI Cohort: An internal safety review committee will review the clinical safety data on a monthly basis for the anti-PD1 and the anti-CTLA-4 cohorts. If the 3 patients for each of the 2 CPI cohorts have been enrolled and demonstrated no negative safety signals after 3 doses of IMM-101, all subsequent patients enrolled to these cohorts will receive the standard, more intense, IMM-101 2 weekly dosing interval for the first induction dosing regimen. If any of the patients in the CPI cohort receiving the Standard IMM-101 Dose Regimen experience any negative safety signals, the cohort will all be switched to the Reduced Intensity IMM-101 Dosing Regimen.