Final Study Protocol for:

Study IMM-101-015

NCT03711188

A Study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor Therapy in Patients with Advanced Melanoma

CONFIDENTIAL
CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor Therapy in Patients with Advanced Melanoma
PROTOCOL NUMBER:	IMM-101-015
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VERSION TABLE

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STATEMENT OF CONFIDENTIALITY

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

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1. GLOSSARY

ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
anti-PD1	anti-programmed cell death-1 receptor
AST	aspartate transaminase
BCG	Bacille Calmette-Guérin vaccine; a preparation of attenuated live *Mycobacterium bovis*
β-hCG	β-human chorionic gonadotropin
BOR	best overall response
CI	confidence interval
CPI	checkpoint inhibitor
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRC	colorectal cancer
CRO	contract research organisation
CRP	C-reactive protein
CT	computerised tomography
CTL	Cytotoxic T lymphocytes
CTCAE	Common Terminology Criteria for Adverse Events
DC	dendritic cells
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EudraCT	European Union Drug Regulating Authorities Clinical Trials: the European Clinical Trials Database of all clinical trials commencing in the European Union from 1 May 2004 onwards
GCP	good clinical practice
GEM	Gemcitabine
GGT	gamma-glutamyl transferase
GLP	good laboratory practice
GMP	good manufacturing practice
GP	general practitioner
Hb	haemoglobin
HIV	Human Immunodeficiency Virus

HR	hazard ratio
IB	investigator's brochure
IBD	International Birth Date
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN-α	interferon-alpha
IMAGE1	**I**mmune **M**odulation **A**nd **G**emcitabine **E**valuation **1**
IMM-101	suspension of heat-killed whole cell *Mycobacterium obuense*
IRB	institutional review board
IV	intravenous
irCR	immune-related Complete Response
irPD	immune-related Progressive Disease
irPR	immune-related Partial Response
irRC	immune-related Response Criteria
irSD	immune-related Stable Disease
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
KM	Kaplan-Meier
LDH	lactate dehydrogenase
M. obuense	*Mycobacterium obuense*
M. vaccae	*Mycobacterium vaccae*
MedDRA	Medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCICTCAE	National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
NCTC	National Collection of Type Cultures
NK	natural killer
NPP	named patient programme
ORR	overall response rate
OS	overall survival
PD1	programmed cell death-1
PDAC	pancreatic ductal adenocarcinoma
PFS	progression free survival

PR	partial response
PP	Per protocol
QA	quality assurance
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software
SBRT	stereotactic body radiation therapy
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamate-pyruvate transaminase (ALT)
SmPC	summary of product characteristics
SOC	standard of care
SOP	standard operating procedure
StD	Standard deviation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organisation
WMA	World Medical Association

2. PROTOCOL SYNOPSIS

Title	A Study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor Therapy in Patients with Advanced Melanoma
Protocol Number	IMM-101-015
EudraCT Number	2018-001346-34
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	Dr Alberto Fusi
Number of Sites	Approx. 3-4 sites
Phase	2a
Indication	Patients with unresectable, Stage III or Stage IV metastatic melanoma who are either previously untreated (cohort A), or whose disease has progressed during PD-1 blockade (cohort B).
Study Rationale	IMM-101 has been studied in 19 patients with advanced melanoma in a Phase 1 dose-escalation study, IMM-101-001. Ten of these patients enrolled in a later follow-up study, IMM-101-008, and continued to receive IMM-101 until study termination in December 2018. The median time on treatment from first dose in study IMM-101-001 was 5.2 years (range 2.7 to 8.0 years). No safety signals were detected from the study with the most common treatment-related adverse events being injection site reactions. IMM-101 has also been studied in a Phase 2 clinical study in advanced pancreatic cancer, IMM-101-002. In this study, IMM-101 administered with gemcitabine (GEM) to 75 patients showed clinically relevant survival benefits and improvements in progression free survival (PFS) compared to GEM alone (35 patients). This was achieved without significant additional toxicity[14]. Immune therapies are important in the treatment of advanced melanoma with the efficacy of checkpoint inhibitors (CPIs) well established. The anti-PD-1 antibody, nivolumab, is recognised as a standard of care for patients with advanced melanoma and has demonstrated improved overall survival (OS), progression-free survival (PFS) and response rates compared to ipilimumab with an objective response rate of 44% (CheckMate 067) [17]. Some patients fail to respond to anti-PD-1 therapy and for these the treatment options are limited. Ipilimumab is approved for previously treated advanced melanoma but response rates following anti-PD-1 treatment failure are low at around 10-15% from retrospective analyses [19] [20]. IMM-101 has demonstrated encouraging pre-clinical activity in combination with CPIs against cancer cell lines and the mode of action, involving the activation of select groups of immune cell types, which are specifically known for being essential in the effective killing of tumour cells and a prerequisite for optimal CPI function, provides rationale for using the combination of IMM-101 with CPIs in a clinical study. This study seeks to investigate whether the combination of IMM-101 with nivolumab is well-tolerated and to investigate efficacy signals of the

	combination, both in treatment-naive patients (cohort A) and in those whose disease has progressed during PD-1 blockade (cohort B). Ipilimumab may be used as a subsequent treatment in place of nivolumab alongside IMM-101 for patients in cohort B either because they continue to progress on study according to RECIST 1.1 and/or investigator decision that continuing to receive nivolumab is no longer appropriate due to clinical progression.
Study Design	During this open-label study, patients who provide written informed consent will participate in a Screening Period to establish eligibility up to a maximum of 21 days prior to enrolling in the study. Once eligibility is confirmed, patients will enter the Treatment Phase of the study and follow the Study Schedule of Assessments. Treatment for patients in both cohorts is continued until disease progression (as assessed by Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) subject to the following qualifications: unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent, or 18 months of study treatment, whichever is the sooner. Patients with a complete response maintained over 2 scans should continue treatment unless the Investigator considered this not in the patient's best interest. Patients in cohorts A and B who have documented disease progression may continue treatment with nivolumab + IMM-101 on study if they have a clinical benefit and no decline in performance status, no clinically relevant adverse effects with the study treatment as determined by the Investigator, or are not deemed to require alternative treatment. Patients in cohort B who fail to respond to treatment with IMM-101 + nivolumab i.e., they have either documented progression by RECIST 1.1, or clinical progression (but without meeting the RECIST 1.1 rules for progressive disease), and, in both cases have no prior recorded response, have the option to change treatment on study to ipilimumab + IMM-101 if the Investigator considers this in the patient's best interest and the patient has not previously received ipilimumab off study (monotherapy or in combination). This treatment may continue until the maximum 4 doses of ipilimumab have been received or stop sooner due to unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of study treatment, whichever is the sooner. Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner. Following baseline assessments, all patients will be followed up for assessment of safety, response to treatment (via scheduled scans) and survival, according to the Study Schedule of Assessments with all patients allowed the opportunity of 18 months of treatment on study. The first post-baseline scheduled scan is at week 12 for patients in cohort A and at week 6 for those in cohort B. Subsequent scans are every 8 weeks with unscheduled scans allowed if clinically indicated, for example to confirm progression. At the discretion of the Investigator, the frequency of scans may be increased to every 12 weeks for patients who continue on study beyond week 52.

	Reviews of all available safety data, to include adverse events (AEs), biochemistry and haematology and injection site reactions, will take place by the Sponsor and Investigator, every 6 months throughout the study. Any signals identified that are believed to impact on patient safety may result in termination of the study. Patients withdrawing from the study or completing the study, where possible, should attend an end of study (EOS) visit. This visit should be within 28±7 days after the final dose of IMM-101 when all previously unresolved AEs will also be followed up. If an end of study visit is not possible any unresolved adverse events and an update on concomitant medications should be followed up by other means of contact (e.g telephone). Patients completing or withdrawing from the study will be followed up for post-study survival information until database lock.

Objectives	The primary objectives of this study are to investigate the effectiveness of IMM-101 combined with nivolumab in controlling advanced melanoma and to assess and describe the safety profile of the combination after a maximum of 18 months of treatment with IMM-101 + nivolumab. The safety and efficacy of the combination will be assessed in patients who are either previously untreated (cohort A), or whose disease has progressed during PD-1 blockade (cohort B) and compared with published data on the efficacy and adverse event profile of nivolumab alone. The primary objectives are: • To evaluate Overall Response Rate (ORR) after a maximum of 18 months treatment, in patients with advanced melanoma receiving IMM-101 + nivolumab. ORR in both previously untreated patients (cohort A) and in patients whose disease has progressed during PD-1 blockade (cohort B) will be evaluated using RECIST 1.1. ORR will also be assessed for subgroups based on PD-L1 status (positive or negative/undetermined) in cohort A patients. • To evaluate the safety and tolerability of the combination of IMM-101 + nivolumab in patients with advanced melanoma by examining the profile of adverse events experienced. The secondary objectives of the study are: • To evaluate Progression-free Survival (PFS) after a maximum of 18 months treatment in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1 • To evaluate Overall Survival (OS) and OS at 1 year in patients with advanced melanoma for both cohort A and cohort B. • To evaluate changes in laboratory parameters • To evaluate local tolerability (injection site reactions) The exploratory objectives are: • To evaluate the ORR in patients with advanced melanoma receiving IMM-101 + nivolumab using immune-related Response Criteria (irRC) for both cohort A and cohort B. • To evaluate the Duration of Response and Time to Response in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1. • To evaluate Disease Control for patients in cohort B of the study only, defined as those patients with a response or stable disease (SD) based on RECIST 1.1. and assessed at each scan assessment point from Week 14 onwards. • To evaluate Best Overall Response (BOR) for patients in cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab, by including all tumour assessments on study. • To evaluate the safety and tolerability of the combination of IMM-101 + ipilimumab in patients with advanced melanoma by examining the profile of adverse events experienced for any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment.

	• Monitoring of selected markers of tumour burden and immunological status in patients receiving IMM-101 (to be reported separately to other endpoints).
Study Duration	The study will continue until all patients have had the opportunity of 18 months treatment on study. 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 post study completion or in the event of withdrawal from the study. These data will be collected until database lock.
Principal Selection Criteria	A patient must meet all of the following inclusion criteria to be eligible to participate in this study: 1. Patient must have a histologically-confirmed diagnosis of advanced (unresectable Stage III) or metastatic (Stage IV) melanoma excluding uveal/ocular melanoma. Patients with unknown primary melanoma are eligible. 2. Patient has at least one measurable lesion by CT or MRI, according to RECIST 1.1. 3. Patient must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing during the Screening Period. 4. Patients who have had prior radiotherapy must have completed this at least 2 weeks prior to study drug administration (Week 0, Visit 1). Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to enrolment (Week 0, Visit 1), and all related adverse events have resolved or stabilised. 5. Patient is considered suitable for treatment with nivolumab. 6. Patient provides signed informed consent for participation in the study. 7. Patient has an Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) Performance Status of ≤1 at Day 0. 8. Patient has Screening laboratory values meeting the following criteria. These should be obtained within 14 days prior to first dose on study: a. Haemoglobin (Hb) ≥9.0g/dL, absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L and White Blood Cells (WBC) ≥ 2.0 x 10^9/L (blood transfusion to achieve these levels are not permitted within 2 weeks of this assessment). 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]), and alanine transaminase (ALT; serum glutamate pyruvate transaminase [SGPT]) each ≤2.5 x ULN or ≤5 x ULN in presence of liver metastases. d. Creatinine ≤1.5 x ULN e. Serum albumin ≥30g/L

	9. Patient is aged ≥18 years. For cohort A, the following inclusion criteria must also be met for a patient to be eligible to participate in this study: *1.* Patient is treatment-naive (i.e. no prior systemic anticancer therapy for unresectable or metastatic melanoma). *2.* Patient must have a tumour sample (archived tissue in the last 3 months or newly obtained biopsy) that is adequate for PD-L1 assessment prior to enrolment. Patients will be eligible to participate regardless of the level of PD-L1 expression. Patients with an inadequate archived sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo one further re-biopsy at the discretion of the investigator. For cohort B, the following inclusion criteria must also be met for a patient to be eligible to participate in this study: *1.* Patient is either currently on (or has previously received) treatment with an anti-PD-1 therapy (monotherapy or in combination), for advanced melanoma and has progressive disease by RECIST 1.1 after at least 3 doses of anti-PD-1 given as monotherapy or at least 2 doses of anti-PD-1 given in combination regimes, and has not received any therapy since, for advanced melanoma. The last dose of PD-1 targeted therapy must have been received no more than 12 weeks prior to the start of Screening but more than 6 weeks prior to first IMM-101 administration. For all patients in cohort B, progression must have occurred during the PD-1 targeted treatment and the investigator has deemed it appropriate to continue/start treatment with nivolumab beyond disease progression. 2. Patients must have recovered from any AEs related to prior anti-PD-1 containing regime to Grade 1 or have resolved. *3.* Patients with a BRAF mutation must have taken BRAF- and/or MEK-targeted therapy, unless patients are not candidates for, or have refused, these therapies. Anti-PD-1 therapy must be the current or last treatment for advanced melanoma prior to study entry.

	A patient meeting any of the following exclusion criteria is not eligible to participate in this study: *1.* Patient has uveal/ocular melanoma. . *2.* Patient has active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible for cohort B of the study only, if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 21 days prior to first dose of study treatment administration. *3.* Patient has previously received treatment with IMM-101. *4.* Patient is either receiving concomitant treatment with another investigational product or has received such treatment within the 3 weeks prior to first IMM-101 administration. *5.* Patient has any serious or uncontrolled medical disorder or co-existing active infection that, in the opinion of the Investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate. *6.* Patient has any previous or concurrent malignancy. Patients will not be excluded if they have had 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 previously experienced an allergic reaction to any mycobacterial product or any monoclonal antibody. *8.* Patient has a history of non-infectious pneumonitis that required steroids or current pneumonitis. *9.* Patient has documented history of clinically severe autoimmune disease or a syndrome that requires systemic steroids or immunosuppressive agents. *10.* Patient has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). *11.* Patient has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected). *12.* Patient has received live vaccine within 30 days before Week 0, Visit 1. *13.* Patient is pregnant or breast-feeding. Female patients with reproductive potential must have a negative serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) within 72 hours prior to first administration of study treatment. 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. *14.* Patient has used depot corticosteroids in the 6 weeks before initiation of Screening (signing of the informed consent form [ICF]).

	15. Patient has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressant drugs (such as azathioprine, tacrolimus, cyclosporin) within the 14 days period before the first administration of IMM-101. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. 16. Patient has received a blood transfusion within 4 weeks prior to initiation of Screening. *17.* In the opinion of the Investigator, the patient is unable or unwilling to comply with the protocol. For cohort A, patients meeting any of the following criteria are also ineligible to participate in this study: *1.* Patient has received prior therapy with an anti-programmed cell death-1 (anti-PD-1), anti-PD ligand-1 (PD-L1), anti-PD-L2, anti-CD137 antibody, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agent. For cohort B, patients meeting any of the following criteria are also ineligible to participate in this study: *1.* Patient has previously experienced an AE related to anti-PD-1 therapy which, in the investigator's opinion, makes them unsuitable for further treatment with nivolumab.
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). Dosing of nivolumab to be in accordance with the prescribing information. Dosing of ipilimumab, when used as subsequent treatment for patients in cohort B, to be in accordance with the prescribing information.
Administration	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. During the study, at the discretion of the Investigator, the dose interval may be modified provided the minimum period between doses is at least 12 days (14±2 days) between visits 1-2, 2-3, 5-6 and 6-7. The 28 day interval ±2 days between other doses (3-5, 7-9 and all after this point) should be maintained, subject to skin reactions or other immune-related AEs as detailed below. IMM-101 is given via intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose. Local skin reactions are expected but, in the event of an injection site reaction of ≥Grade 3 (severe) as measured by the NCI CTCAE v4.03, 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) 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 4 weeks.

	Nivolumab is to be administered in accordance with the prescribing information. When the patient starts on the study, the Investigator can choose to administer nivolumab using one of the following dosing regimens – 3mg/kg every 2 weeks, 240mg every 2 weeks or 480mg every 4 weeks. Ideally, the nivolumab dosing regimen chosen at the start of the study should be maintained (notwithstanding modifications due to AEs as described above). However, if a 480mg 4-weekly nivolumab dosing is not tolerated, the patient may be switched to a 240mg 2 weekly regimen. In instances when nivolumab and IMM-101 are given on the same day, IMM-101 will be administered first. If used on study for patients in cohort B, ipilimumab is to be administered every 3 weeks in accordance with the prescribing information. In instances when ipilimumab and IMM-101 are given on the same day, IMM-101 will be administered first. In the event of any immune-mediated adverse reactions of ≥ Grade 3 (severe), IMM-101 and nivolumab (or ipilimumab when used for cohort B) should be withdrawn, either until resolution of the event or permanently, at the discretion of the Investigator.
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. No antineoplastic systemic chemotherapy or biological therapy are allowed and live vaccines and other investigational agents are also not permitted. Radiation therapy, apart from to a single solitary lesion after the first scheduled tumour assessment on study, should not be used.
Visit Schedule	The study will consist of two phases – Screening Phase and Treatment Phase. Details of the Study Schedule are shown in Appendix 1.
Safety and Tolerability Endpoints:	The primary safety endpoint is: • Incidence, frequency and severity of AEs, SAEs, treatment related AEs, immune-related AEs, Grade 3 and above AEs and AEs leading to IMM-101 discontinuation or study withdrawal experienced during treatment with IMM-101 + nivolumab for both cohorts Secondary safety endpoints are: • Incidence and frequency of laboratory parameter abnormalities • Change from baseline values in laboratory parameter values • Incidence and frequency of local injection site reactions. An exploratory safety endpoint is: For any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment, the incidence, frequency and severity of AEs, SAEs, treatment related AEs, and immune-related AEs from the start of treatment with ipilimumab.
Efficacy Endpoints:	The primary efficacy endpoint is: • Overall Response Rate (ORR) calculated from the BOR of patients as assessed by RECIST 1.1. ORR will be assessed at the end of study or when all patients have withdrawn, if this is sooner. For cohort B, ORR will apply to BOR from tumour assessments during IMM-101 + nivolumab treatment only. ORR and BOR will also be assessed for

	subgroups based on PD-L1 status (positive or negative/undetermined) in cohort A patients. The secondary efficacy endpoints of this study are: • Progression-free survival (PFS) assessed by RECIST 1.1 after a maximum of 18 months treatment in patients receiving IMM-101 + nivolumab. • Overall survival (OS) and OS at 1 year, for both cohort A and cohort B. The median OS (if applicable) and OS rate at 12 months will be estimated. Exploratory efficacy endpoints are: • ORR using irRC in patients in both cohort A and cohort B receiving IMM-101 + nivolumab. • Duration of Response and Time to Response for both cohort A and cohort B receiving IMM-101 + nivolumab and assessed by RECIST 1.1. • Disease Control, for patients in cohort B of the study only and defined as those patients with a response or stable disease based on RECIST 1.1., assessed at each scan assessment point from Week 14 onwards. • BOR for cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab. • Immunological markers from blood and biopsy samples (to be reported separately to other endpoints).
Statistical Methods/Sample Size	Sufficient patients will be screened for 18 patients to be enrolled into cohort A and 8 into cohort B of this open-label study. Patients withdrawn during the course of the study will not be replaced. No formal sample size calculation has been performed and the sample size is considered a sufficient and adequate number of patients to investigate the efficacy signals of IMM-101 combined with nivolumab in controlling advanced melanoma and to explore the safety profile of the combination therapy. Evaluation of safety and efficacy will be assessed by cohort. All endpoints will be presented descriptively, and no formal statistical analysis is planned. The statistical methods used will be appropriate to the objectives of the study and the nature of the data and will be described in a statistical analysis plan. The efficacy and tolerability endpoints will be evaluated using the Intent-to-treat (ITT) set, defined as all patients receiving at least one administration of IMM-101, irrespective of compliance with eligibility and other protocol criteria. This set will also define the Safety set. In addition, a Per-protocol (PP) set, defined as ITT patients with no major protocol deviations and having complied with the treatment regimens of the combination therapy, will be used to evaluate further the efficacy of the combination therapy. The study population of each cohort will be described descriptively in terms of baseline demographics, disease history and status, prior and concomitant medication and exposure, compliance and treatment

	modifications with IMM-101 and nivolumab and those with IMM-101 and ipilimumab where relevant for patients in cohort B. Descriptive evaluation of the efficacy and safety endpoints will be performed using summary statistics for continuous data endpoints and frequency counts and percentages for categorical data endpoints. All AEs and procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) drug dictionary and all concomitant treatments will be coded using the World Health Organisation (WHO) Drug Dictionary. All study data will be presented as data listings. Exact binomial confidence intervals (CIs) will be calculated for the observed incidence of ORR (using RECIST 1.1 and irRC criteria). and disease control (cohort B only). Progression free survival (RECIST 1.1) and overall survival will be summarised by Kaplan-Meier (KM) methods and presented graphically. The median OS and 1-year OS rate will be estimated for both cohorts. In addition, by cohort interim data reviews will be conducted for ORR (RECIST 1.1) and incidence, frequency and severity of AEs, when all patients have had the opportunity for 1 year on study (cohort A) and after 6 months on study (cohort B). The by-cohort interim data reviews and/or final analysis may be conducted for each cohort separately or together, depending on recruitment rates.

3. BACKGROUND INFORMATION

This proposed study seeks to investigate whether the combination of IMM-101 with nivolumab is well-tolerated and to investigate efficacy signals of the combination, both in treatment-naive patients (cohort A) and in those whose disease has progressed during PD-1 blockade (cohort B).

Ipilimumab may be used as a subsequent treatment alongside IMM-101 for patients in cohort B either because they continue to progress on study according to RECIST 1.1 or investigator decision that continuing to receive nivolumab is no longer appropriate due to clinical progression.

Safety and tolerability of IMM-101 has previously been assessed in 6 clinical studies:

- **IMM-101-001** was a first-in-human, open-label, dose-escalation, intra-patient, placebo-controlled study, in adult patients with confirmed diagnosis of stage III or IV melanoma to evaluate the safety and tolerability of three doses of IMM-101. The study also characterised local responses to this immunotherapeutic agent in order to delineate unexpected/unacceptable local reactions from those indicative of an appropriate immunological response in this patient group.
- **IMM-101-002** was a randomised, open-label, proof of concept Phase 2 study of the combination of IMM-101 and Gemcitabine (GEM) versus GEM monotherapy as first-line treatment for advanced pancreatic cancer.
- **IMM-101-002A** was a long-term follow-up of patients who completed study IMM-101-002, allowing for continued treatment with IMM-101 for patients from the IMM-101 treated group of the main study. Completing patients from the GEM monotherapy group could also enrol and begin treatment with IMM-101. In this study, patients were allowed to receive any chemotherapeutic therapy alongside IMM-101 at the investigator's discretion and a variety of treatment regimes in combination with IMM-101 were used.
- **IMM-101-008** was an open-label long-term safety follow-up study for patients with melanoma previously enrolled in study IMM-101-001.
- **IMM-101-007** was a Phase 2 single arm investigative study of IMM-101 in combination with stereotactic body radiation therapy (SBRT)-induced tumour necrosis in patients with previously treated colorectal cancer (CRC).
- **IMM-101-011** was a Phase 1/2a open-label study of IMM-101 in combination with selected standard of care regimens in patients with metastatic cancer or unresectable cancer at study entry.

Results of these studies are discussed briefly in Section 3.3; full details are available in the IMM-101 Investigator's Brochure (IB).[1]

Pre-clinical *in vitro* and *in vivo* studies have shown that IMM-101 has effects on the immune system. These observed effects are hypothesised to be the basis for anti-tumour action, beneficial to this patient population. The main effects thought to be crucial for enhancing the anti-tumour immune response are:

- IMM-101 is a strong activator of dendritic cells (DCs) leading to a Type-1 immune response, with formation and activation of $CD8^+$ cytotoxic T lymphocytes (CTLs) and increased production of the cytokine interferon-γ (IFN-γ) in the lymph nodes in which IMM-101 stimulated DCs reside.

- As part of the DC-induced Type-1 immune response, IMM-101 also increases the number and activation of IFN-γ producing (i) type 1 $CD4^+$ helper T cells (Th1), (ii) natural killer cells (NK cells) and (iii) T cells expressing gamma/delta receptors (γδ-T cells).

3.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

IMM-101 is a suspension of heat-killed whole cell *Mycobacterium obuense (M. obuense)* sourced from the National Collection of Type Cultures (NCTC) with reference NCTC 13365 in borate-buffered saline, produced in accordance with good manufacturing practice (GMP) for intradermal administration to humans.

3.2 NON-CLINICAL FINDINGS

Guinea pig sensitisation assays and results from non-clinical safety studies performed in accordance with Good Laboratory Practice (GLP), together suggest that IMM-101 can be safely administered to humans by the intradermal route. The maximum tolerated dose has been defined for both sexes in rats and the No Observed Toxic Effect Level has remained at 0.2 mg/kg after six months dosing.

Experiments with mouse and human immune cells have shown that IMM-101 is a strong activator and antigen processing enhancer of dendritic cells (DCs) and that this activation leads to a typical Type-1 immune response, with formation and activation of Th1 and $CD8^+$ CTLs and increased production of the cytokine IFN-γ in the lymph nodes in which IMM-101 activated DCs reside[2][3][4][5][6]. These and other experiments have also shown that IMM-101 increases the number and activation of NK cells and γδ-T cells[3] [7]. CTLs, NK cells and γδ-T cells are well-known to play crucial roles in anti-tumour responses and attack the tumour through different tumour specific targets. In addition, it has been shown that the presence of activated DCs eliciting Type-1 immune responses is a prerequisite for checkpoint inhibitors (CPIs) to be effective[8]. Together these mechanisms form the basis for the anti-tumour response of IMM-101 and the prediction that the combination of IMM-101 with CPIs will result in a further enhancement of the anti-tumour response, without a significant increase of toxicity often found with other CPI combinations.

In preclinical models, IMM-101 is able to induce protective responses in a host challenged with cancer and limit disease progression. In an *in vivo* model of lung metastasis using CT26 tumour cells injected intravenously, IMM-101 had a strong effect on the metastatic capacity of tumour cells, as IMM-101 treated mice showed a significant reduced metastatic burden. This effect is highly likely to be immune mediated based on observed alterations to immunological properties measured following *in vitro* cell culture analysis including significantly enhanced production of IFN-γ from splenocytes following *in vitro* stimulation with anti-CD3[9].

Experiments have been carried out in two well-validated clinically relevant murine models of pancreatic cancer, which mirror histologically human pancreatic ductal adenocarcinomas (PDAC) with moderately differentiated ductal morphology and extensive stromal desmoplasia[10] [11]. In these models, IMM-101 showed anti-tumour activity and increase of $CD8^+$ T cells inside the tumours[12].

In a murine model with the breast cancer cell line EMT-6, IMM-101 increased the response to anti-PD1 antibodies, resulting in a slower growth of tumour volume, an increase in the intra-tumour $CD8^+$ T cells/Treg ratio and an increase of the IFN-γ/IL-10 ratio in spleen cells compared to anti-PD1 alone [4]. In similar mice experiments using murine KPC pancreas cancer cell lines it was found that the combination treatment of IMM-101 with an anti-PD-L1 or an

anti-CTLA-4 agent had significantly stronger anti-tumour effects than the CPI or IMM-101 alone. Furthermore, although no decrease of tumour volume was observed in a murine model with the highly aggressive B16 melanoma tumour, the combination of IMM-101 with PD1 antibody treatment increased the ratio of the numbers of $CD8^+$ T effector cells divided by the numbers of immune suppressing T-regulatory cells inside the tumour. An increase in this ratio is suggestive for an increase in anti-tumour activity[13].

Further non-clinical details can be found in the IB.[1]

3.3 CLINICAL FINDINGS

Please see the Reference Safety Information in Section 8 of the IMM-101 IB[1] for information on expected serious adverse reactions to the administration of IMM-101 and Section 7.3 for information on adverse reactions across all clinical studies.

3.3.1 Study Number IMM-101-001

IMM-101 was evaluated initially in an open-label, dose-escalation, intra-patient placebo-controlled study (IMM-101-001), in 19 adult patients with confirmed diagnosis of stage III or IV melanoma and in remission. The study was initiated in 2010 and evaluated the safety and tolerability of three doses of IMM-101 (0.1 mg, 0.5 mg and 1.0 mg).

There were no dose limiting toxicities observed and no evidence to suggest a clinically significant impact upon haematological indices, biochemical parameters, vital signs or cardiac function. The adverse events (AE) observed with IMM-101 were in line with expectations, manageable and in keeping with data from non-clinical models and past experience in humans with other heat-killed whole cell mycobacterial preparations (*M. vaccae)*. The injection site reactions were consistent for this class of product and were well tolerated by the patients.

3.3.2 Study Number IMM-101-008

Following the completion of Study IMM-101-001, the majority of subjects continued to receive IMM-101 on a 'named patient' basis to allow continued administration of IMM-101. However, given the limited amount of safety data that can be collected in a 'named patient' context, a follow-up study, IMM-101-008, was initiated in February 2012. Ten subjects (9 stage IV, 1 stage IIIc) previously enrolled in IMM-101-001 provided informed consent and entered this follow-up study. By September 2018 patients had been receiving IMM-101 periodically for up to 8 years since first receiving IMM-101 in study IMM-101-001, with four long term survivors remaining on study. Of the other 6 patients, 3 had withdrawn and 3 had died on study. This study provided important information regarding the safety and tolerability of long-term administration of IMM-101 and some anecdotal information about the efficacy. However, the Sponsor anticipated that no further meaningful data would be collected in the context of this study to address the primary objective of determining the long-term safety profile of IMM-101 administered intradermally for extended use. It was therefore decided to terminate the study early in December 2018. At database lock in April 2019 median time on treatment from first dose in study IMM-101-001 was confirmed as 5.2 years (range 2.7 to 8.0, n=10).

Three serious adverse events (SAE) occurred on study, none considered related to IMM-101. Of the 27 AEs considered related to IMM-101 treatment, 91% fell under the category of injection site reactions (including events coded to injection site ulcer, injection site erythema, injection site infection, injection site necrosis, injection site pain and injection site swelling). Five of the 10 patients received concomitant anti-melanoma cancer therapy alongside IMM-101, including surgery, chemotherapy, radiotherapy and immunotherapy.

3.3.3 Study Number IMM-101-002 and IMM-101-002A

In May 2011, IMM-101-002, (IMAGE1, **I**mmune **M**odulation **A**nd **G**emcitabine **E**valuation **1**) a randomised, open-label, proof of concept, Phase 2 study comparing GEM, with and without IMM-101, as first-line treatment for advanced pancreatic cancer was initiated. The study recruited patients at 20 sites in the United Kingdom (UK), Spain, Italy, Ireland and Cyprus over a 2-year period ending in August 2013. A total of 110 patients were randomised: 75 to the IMM-101 plus GEM group, 35 to the Control (GEM alone) group. This study has now reported. The safety and efficacy data are presented in the IMM-101 IB[1].

The median overall survival (OS) was 6.7 months for the IMM-101 treated group and 5.6 months for the Control group (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.44, 1.04; p = 0.076). For the subgroup of patients with metastatic disease (84% of population), the median OS was 7.0 months for the IMM-101 treated group and 4.4 months for the Control group (HR 0.54; 95% CI 0.33, 0.87; p = 0.011). Median progression-free survival (PFS) was also improved for the IMM-101 treated group at 4.1 months for the IMM-101 treated group and 2.4 months for the Control group (HR 0.58; 95% CI 0.37, 0.91; p = 0.018). For the subgroup of patients with metastatic disease, the median PFS was 4.4 months for the IMM-101 treated group and 2.3 months for the Control group (HR 0.46; 95% CI 0.28, 0.75; p = 0.002). Baseline factors analysed were not found to have any statistically significant impact on the efficacy results.

The frequency of AEs was similar in the IMM-101 treated group compared to the Control group (3.05 AEs per month on study for the IMM-101 treated group and 3.59 AEs for the Control). The most common adverse events of Grade 3 or higher were asthenia (10.8% in the IMM-101 treated group and 2.9% in the Control group, fatigue (5.4% v. 11.4%), white blood cell count decreased (2.7% v. 11.4%) and neutropenia (14.9% v. 11.4%).

Injection site reactions, viewed as a normal and predicted reaction to exposure to a preparation of mycobacterial antigens, were consistent for this class of product and were well tolerated by the patients.

Patients who completed study IMM-101-002 were invited to enrol in the long-term follow-up Sub-Study, IMM-101-002A, which allowed for treatment with IMM-101, regardless of which treatment group the patient had been randomised to in IMM-101-002. Chemotherapy treatment could be prescribed at the Investigator's discretion. Twelve patients who completed IMM-101-002 were enrolled in this Sub-Study. Of these, 11 patients had been randomised to the IMM-101 treated group and 1 patient had been randomised to the Control group in the IMM-101-002 Main Study.

Additional survival analysis from the IMM-101-002 study, incorporating all data from IMM-101-002A at database lock, gave a survival probability for the IMM-101 treated group of 20.3% at 12 months, 15.4% at 18 months, 9.7% at both 24 and 30 months and 4.8% at 36 months. For the Control group, the survival probability was 15.8% at 12 months and 1.8% at 18 months with no survival data beyond this point. Median values for OS and PFS were unchanged from those previously reported for the Main Study. Maximum exposure to IMM-101in IMM-101-002A was 34.3 months, with a maximum exposure over the combined IMM-101-002 and IMM-101-002A studies of 46.5 months. Individual adverse event types of Grade 3 or higher occurred with incidence of no more than one patient in IMM-101-002A.

Results from the IMM-101-002 study have been published[14]. Please also refer to the IB for further details[1].

3.3.4 Study Number IMM-101-007

In June 2012, a Phase 2, single-arm, investigative study of IMM-101 in combination with SBRT-induced tumour necrosis, in patients with previously treated colorectal cancer was initiated at two sites in the UK (IMM-101-007). The IMM-101-007 study was completed in accordance with the protocol after 12 patients were recruited into the first part of the study. Progression to the second part of the Simon 2-stage design, in which a further 19 patients would have been recruited, required an objective response or stabilisation of disease at 24 weeks in at least one of the first 12 patients. This was not observed so the second stage of the study was not initiated and no further patients were enrolled.

It was not possible to demonstrate any synergy between immunomodulation with IMM-101 and SBRT in this small pilot study in this chemotherapy-refractory advanced metastatic colorectal cancer population. IMM-101 was well tolerated in this study with no new safety signals detected.

3.3.5 Study Number IMM-101-011

Study IMM-101-011 was a novel Phase 1/2a open-label study of IMM-101 in combination with selected standard of care regimens in patients with metastatic cancer or unresectable cancer at study entry. The study was terminated early in August 2017 due to a re-evaluation by the Sponsor of its clinical development plan. Two patients with metastatic melanoma were enrolled on the study and both received 3 doses of IMM-101 together with nivolumab. At the end of study, response was assessed by immune-related response criteria (irRC) with one patient having a partial response and the other having stable disease at scans taken close to week 11. One of the patients experienced 4 adverse events while on study which were all mild or moderate in nature, non-serious, and all resolved by the end of study. The other patient had no adverse events. Both patients continued to receive IMM-101 on the Named Patient Programme after the end of study.

3.4 RATIONALE

The incidence of malignant melanoma is reported to be increasing every year, both globally and in the UK. The mortality associated with advanced melanoma remains high with 1 year survival rates for those diagnosed with stage IV melanoma between 2013 and 2017 being 51% for males and 56% for females in England[15][16]. Five-year net survival for melanoma skin cancer shows a large difference in survival between Stages I (99%) and III (71%). In females, five-year net survival at Stage III is 74% and in males 68% for patients diagnosed during 2013-2017 in England [15][16].

Treatment options have increased in recent years with the development of immunotherapies (ipilimumab, nivolumab and pembrolizumab) and targeted therapies blocking BRAF and MEK. In Phase 3 studies, the anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab, have demonstrated superiority to ipilimumab as first-line treatment for patients with advanced melanoma with overall response rates of 44% for nivolumab (treatment-naive patients)[17] and 33% for pembrolizumab (one prior treatment allowed)[18]. However, a certain proportion of patients fail to respond to anti-PD-1 therapy with 56% of patients failing to show a response to nivolumab and 67% failing to respond to pembrolizumab in the Phase 3 trials[17] [18]. For patients whose disease continues to progress on anti-PD-1 therapy, the treatment options are limited and ipilimumab is frequently the second-line therapy of choice although overall response rates in the second-line setting are only 10-15% (analysed retrospectively)[19] [20].

The clinical studies with IMM-101 to date have shown promising efficacy signals in metastatic

pancreatic cancer and the long-term survival of some patients with advanced melanoma in study IMM-101-008 is encouraging[21]. It is therefore appropriate to study the efficacy and safety of IMM-101 in advanced melanoma further, alongside the first-line treatment in current use. This is also suggested by the good results of a few advanced melanoma patients that used IMM-101 prior to starting CPI treatment[22]. Results from pre-clinical work showing improved activity of IMM-101 in combination with CPIs compared to the activity of either single agent (Section 3.2) provides encouragement for using the combination. In addition, an important feature of the mode of action of IMM-101 is its ability to activate and mature immature DCs into a sub-class of dendritic cells that elicit Type-1 immune responses (known as cDC1s). It has been shown that activation of sufficient numbers of cDC1s is a prerequisite for CPIs to be effective[8], providing further rationale for using the combination of IMM-101 with CPIs in a clinical study.

Anti-PD-1 therapies may be associated with adverse events that have an immunological cause with the most common adverse events observed in Phase 3 trials being skin-related conditions such as rash and pruritus and gastrointestinal events such as diarrhoea. Fatigue was the most common adverse event seen for both nivolumab and pembrolizumab.

IMM-101 has been well tolerated overall in clinical studies to date, including over extended dosing periods for some patients. The only treatment-related adverse events to have occurred in more than 10% of patients when analysed across all clinical studies to date are pyrexia (10.2%) and injection site reactions (14.8%). Analysis of treatment-related adverse events across all IMM-101 clinical trials does not indicate any appreciable incidence of events with any obvious immunological cause (2.8% incidence of rash, 2.8% incidence of diarrhoea, others in this category below 2%; details in the IB)[1]. Adverse events from the two patients who received IMM-101 and nivolumab in study IMM-101-011, albeit for only 12 weeks, did not give cause for concern that the combination may cause an exacerbation of immune mediated toxicities.

Study IMM-101-015 seeks to investigate the safety and efficacy of IMM-101 in combination with nivolumab, both in treatment-naïve patients (cohort A) and in those patients whose disease has progressed during anti-PD-1 therapy (Cohort B). Patients in cohort B have the option to remain on study and change therapy to ipilimumab and IMM-101 if their disease continues to progress.

3.5 POTENTIAL RISKS AND BENEFITS

Clinical studies with IMM-101 to date have shown promising efficacy signals in metastatic pancreatic cancer and encouraging indications of long-term survival in both this indication and in patients with advanced melanoma. To date, the only adverse drug reactions associated with IMM-101 treatment that have occurred in more than 10% of patients in clinical studies are injection site reactions (14.8%) and pyrexia (10.2%) both of which can be viewed as predicted reactions to exposure to a preparation of mycobacterial antigens[1]. The injection site reactions are consistent for this class of product and have been well tolerated by patients to date in the context of both the Phase 1 and Phase 2 studies, including over extended administration periods of over 2 years in 13 patients.

Clinical experience over this time suggests that repeated administration is well tolerated initially on a monthly administration regimen, however, the incidence and severity of injection site reactions increases over time, and a reduction in dose and/or an increase in the dosing interval may be required after prolonged administration. In IMM-101-002A, 8 of the 12 patients received only full doses (i.e. did not have any dose reduction) over the combined IMM-

101-002/002A study period with the maximum number of full doses received being 31 and few dosing delays. In study IMM-101-008, many patients received half doses after 1 year on study but this was following IMM-101 treatment in IMM-101-001 and on a named patient basis.

Therefore, the Investigator will closely supervise the patients and in the event of unexpectedly severe or long-lasting site reactions will inform the Sponsor and reduce the dose, or delay administration or withdraw the patient from the study after consultation with the Sponsor.

4. STUDY OBJECTIVES AND PURPOSE

The primary objectives of this study are to investigate the effectiveness of IMM-101 combined with nivolumab in controlling advanced melanoma and to assess and describe the safety profile of the combination after a maximum of 18 months treatment. The safety and efficacy of the combination will be assessed in patients who are either previously untreated (cohort A), or whose disease has progressed during PD-1 blockade (cohort B) and compared with published data on the efficacy and adverse event profile of nivolumab alone.

4.1 PRIMARY OBJECTIVES

- To evaluate Overall Response Rate (ORR) after a maximum of 18 months treatment in patients with advanced melanoma receiving IMM-101 + nivolumab. ORR in both previously untreated patients (cohort A) and in patients whose disease has progressed during PD-1 blockade (cohort B) will be evaluated using RECIST 1.1. ORR will also be assessed for subgroups based on PD-L1 status (positive or negative/undetermined) in cohort A patients.
- To evaluate the safety and tolerability of the combination of IMM-101 + nivolumab in patients with advanced melanoma by examining the profile of adverse events experienced.

4.2 SECONDARY OBJECTIVES

- To evaluate Progression-free Survival (PFS) after a maximum of 18 months treatment in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1
- To evaluate Overall Survival (OS) and OS at 1 year in patients with advanced melanoma for both cohort A and cohort B.
- To evaluate changes in laboratory parameters.
- To evaluate local tolerability (i.e. injection site reactions).

4.3 EXPLORATORY OBJECTIVES

- To evaluate the ORR in patients with advanced melanoma receiving IMM-101 + nivolumab using irRC for both cohort A and cohort B.
- To evaluate the Duration of Response and Time to Response in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1.
- To evaluate Disease Control for patients in cohort B of the study only, defined as those patients with a response or stable disease based on RECIST 1.1 during treatment with IMM-101 + nivolumab. To be assessed from response data at Week 14 and at 8 weekly intervals thereafter.
- To evaluate BOR for patients in cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab.
- To evaluate the safety and tolerability of the combination of IMM-101 + ipilimumab in patients with advanced melanoma by examining the profile of adverse events experienced for any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment.
- Monitoring of selected markers of tumour burden and immunological status in patients receiving IMM-101 (to be reported separately to other endpoints).

5. STUDY DESIGN AND ENDPOINTS

5.1 STUDY DESIGN

IMM-101-015 is an open-label Phase 2a study to investigate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors in patients with advanced unresectable Stage III or Stage IV metastatic melanoma who are either previously untreated (i.e. no prior systemic anticancer therapy for unresectable or metastatic melanoma; cohort A), or whose disease has progressed during PD-1 blockade (cohort B).

Patients suitable for enrolment to cohort B are currently receiving, or have previously received, treatment with an anti-PD-1 therapy (monotherapy or in combination) for advanced melanoma and have progressive disease by RECIST 1.1 after at least 3 doses of anti-PD-1 given as monotherapy or at least 2 doses of anti-PD-1 given in combination regimes, and have not received any therapy since, for advanced melanoma. The last dose of anti-PD-1 therapy must have been received no more than 12 weeks prior to the start of Screening but more than 6 weeks prior to first IMM-101 administration. For all patients in cohort B, progression must have occurred during the PD-1 targeted treatment and the investigator must have deemed it appropriate to continue/start treatment with nivolumab beyond disease progression.

Treatment for patients in both cohorts is continued until disease progression as assessed by RECIST 1.1 subject to the qualifications below, unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of study treatment, whichever is the sooner. Patients with a complete response maintained over 2 scans should continue treatment unless the investigator considered this is not in the patient's best interest.

Patients in cohorts A and B who have documented disease progression (RECIST 1.1) during the study may continue treatment with IMM-101 + nivolumab on study if they have a clinical benefit and no decline in performance status, no clinically relevant adverse effects with the study treatment as determined by the investigator, and are not deemed to require alternative treatment.

Patients in cohort B who fail to respond to treatment with IMM-101 + nivolumab i.e., they have either documented progression by RECIST 1.1, or clinical progression (but without meeting the RECIST 1.1 rules for progressive disease), and, in both cases have no prior recorded response, have the option to change treatment on study to ipilimumab + IMM-101 if the Investigator considers this in the patient's best interest and the patient has not previously received ipilimumab off study (monotherapy or in combination). This treatment may continue until the maximum 4 doses of ipilimumab have been received or stop sooner due to unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of study treatment, whichever is the sooner. Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner.

All patients will be followed up for assessment of safety, response to treatment (via scheduled computerised tomography [CT] or magnetic resonance imaging [MRI scans]) and survival, according to the Study Schedule of Assessments with all patients allowed the opportunity of 18 months of treatment on study. The first scheduled post-baseline scan is at week 12 for patients in cohort A and at week 6 for those in cohort B. Subsequent scans are every 8 weeks with unscheduled scans allowed if clinically indicated, for example to confirm progression. At

the discretion of the Investigator, the frequency of scans may be increased to every 12 weeks for patients who continue on study beyond week 52.

Reviews of all available safety data, to include AEs, biochemistry and haematology and injection site reactions, will take place by the Sponsor and Investigator every 6 months throughout the study. Any signals identified that are believed to impact on patient safety may result in termination of the study.

This Phase 2a open-label study will consist of two phases:

1. Screening and Enrolment

   Patients who provide informed consent will participate in a screening period of up to a maximum of 21 days to establish eligibility. Once eligibility is confirmed a full disease and treatment history will be taken.

   Given the need in this study to relate efficacy to PD-L1 status for patients in cohort A, a tumour sample from an unresectable or metastatic site of disease must be provided that is adequate for PD-L1 assessment prior to enrolment. The tumour sample will be collected during Screening for all patients in cohort A for PD-L1 expression testing unless archived tissue obtained in the preceding 3 months is available. Patients will be eligible to participate regardless of the level of PD-L1 expression. Patients with an inadequate archived sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo re-biopsy on a further single occasion at the discretion of the Investigator.

2. Treatment Phase

   All patients who are confirmed as eligible to participate in the study, and, for female participants who are not surgically sterilised or post-menopausal, have a negative pregnancy test confirmed within 72 hours of first dosing with IMM-101, will enter the Treatment Phase of the study. All patients in both cohorts of the study will receive one 1.0 mg (0.1 mL) dose of IMM-101 every 2 weeks for the first 3 doses followed by a rest period of 4 weeks, then every 2 weeks for the next 3 doses, and thereafter every 4 weeks.

   Nivolumab is given every 2 or 4 weeks (dependent on Investigator choice of dosing regimen) to patients in both cohorts of the study.

   In instances when nivolumab and IMM-101 are given on the same day, IMM-101 will be administered first (see Section 7.6.1).

   If used on study for patients in cohort B, ipilimumab is administered every 3 weeks to a maximum of 4 doses. In instances when ipilimumab and IMM-101 are given on the same day, IMM-101 will be administered first (see Section 7.6.2).

   At the discretion of the Investigator the dose of IMM-101 may be adjusted and dosing of IMM-101, nivolumab or ipilimumab delayed according to local skin reactions to IMM-101 and toxicities to all study drugs as detailed in section 7.2.1.

   The Treatment Phase will continue for up to the Week 78 visit unless such therapy is contraindicated, the patient does not wish to continue, or the study is terminated by the Sponsor.

   Patients will be assessed for response via scheduled scans with the first post-baseline scan at week 12 for patients in cohort A and at week 6 for those in cohort B. Subsequent scans are every 8 weeks with unscheduled scans allowed if clinically indicated, for example to confirm progression. At the discretion of the Investigator, the frequency of

scans may be increased to every 12 weeks for patients who continue on study beyond week 52.

Patients may choose to withdraw from the study at any time and for any reason. Full details of reasons for discontinuation are in section 6.3.

Patients who discontinue study treatment or complete the study should, where possible, attend an end of study visit within 28±7 days after the final dose of IMM-101 when all previously unresolved adverse events will also be followed up. If an end of study visit is not possible any unresolved adverse events and update on concomitant medications should be followed up by other means of contact (e.g. telephone; Section 9.5).

Patients completing or withdrawing from the study will be followed up for survival information until database lock. Any patients who discontinue study treatment for reasons other than progression, and for whom no further treatment is deemed appropriate or desired, should remain on study and have scheduled scans until documented progression.

5.2 ENDPOINTS

5.2.1 Primary Endpoints

This study has two primary endpoints to measure the two primary objectives of evaluating the safety and the efficacy of the IMM-101 + nivolumab treatment combination.

Safety and Tolerability is measured by:

- Adverse events, graded and recorded throughout the study according to NCICTCAE, version 4.03. The incidence, frequency and severity of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for nivolumab) during treatment with IMM-101 + nivolumab will be assessed.

Efficacy is measured by:

- Overall Response Rate (ORR), calculated from the Best Overall Response (BOR) of patients as assessed by RECIST 1.1. ORR is defined as the number of patients with a BOR of CR or PR divided by the number of enrolled patients in each cohort of the study. The BOR is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the Investigator, recorded from the first post-baseline scan until and including the last scan prior to, or at, the end of study treatment for each patient on study. For any patients in cohort B of the study who change treatment on study to IMM-101 + ipilimumab, BOR will be assessed only until the point of this change in therapy.
  In addition, for patients in cohort A, BOR and ORR are assessed after all patients have had the opportunity for 1 year on study (using data from scans obtained up to this time point for each patient), and again at the end of study or when all patients in this cohort have withdrawn, if this is sooner. For patients in cohort B, BOR and ORR are assessed after all patients have had the opportunity for 6 months on study (using data from scans obtained up to this time point for each patient, or until the point of change of therapy to IMM-101 + ipilimumab where applicable) and again at the end of study or when all patients in this cohort have withdrawn, if this is sooner. ORR and BOR will also be assessed for subgroups based on PD-L1 status (positive or negative/undetermined) for cohort A patients at the end of the study.

Evaluation of the primary endpoints will take place when all patients have had the opportunity for a maximum of 18 months study treatment in each cohort. An interim data review on each respective cohort will be conducted after all cohort B patients have had 6 months on study (cohort B), and when all cohort A patients have had the opportunity for 12 months on study.

5.2.2 Secondary Endpoints

The secondary endpoints of this study, to provide further information on the safety and efficacy of the IMM-101 + nivolumab combination, are assessed at the end of the study and measured by:

Progression-free survival (PFS) assessed by RECIST 1.1. PFS is defined as the time between the date of the first post-Screening visit (Week 0, Visit 1) and the first date of documented progression, as determined by the Investigator from CT or MRI scan, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumour assessment. Patients who did not have any on study tumour assessments (scans) and did not die will be censored on their date of first post-Screening visit. Patients in cohort B who change therapy on study to IMM-101 + ipilimumab without documented progression by RECIST 1.1 will be censored at the date of their last evaluable tumour assessment prior to this change in therapy.

Overall survival (OS) and OS at 1 year. OS is defined as the time from enrolment (date of the first post-Screening visit (Week 0, Visit 1) to death due to any cause. Patients without a death date will be censored at the date the patient was last known to be alive. The median OS (if applicable) and OS rate at 12 months will be estimated.

- Incidence and frequency of laboratory parameter abnormalities
- Change from baseline values in laboratory parameter values
- Incidence and frequency of local injection site reactions.

5.2.3 Exploratory Endpoints

The following additional exploratory endpoints, will be assessed at the end of the study and are:

- ORR using irRC for both cohort A and cohort B, assessed using BOR by irRC, with the same methods of calculation as for the primary endpoint of ORR (above).
- Duration of Response and Time to Response for both cohort A and cohort B, assessed by RECIST 1.1. For any patients in cohort B who change treatment on study to IMM-101 + ipilimumab, only responses evaluated until the point of this change in therapy are included.
- Disease Control, assessed for patients in cohort B of the study only, and defined as those patients with a response (CR or PR) or SD based on RECIST 1.1. and assessed at each scan assessment point from Week 14 onwards. Disease Control is evaluated for treatment with IMM-101 + nivolumab only and for any patients who change treatment to IMM-101 + ipilimumab, disease control is assessed until and including the last evaluable tumour assessment prior to the change in therapy.

- For the subgroup of patients in cohort B who receive IMM-101 + ipilimumab as subsequent treatment: the incidence, frequency and severity of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for ipilimumab) experienced following the start of ipilimumab treatment up to the end of the study.
- To evaluate BOR for cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab. All tumour assessments on study are included in this evaluation.
- Immunological markers from blood and biopsy samples from both cohorts A and B (to be reported separately to other endpoints).

5.3 ASSESSMENT OF RESPONSE

Baseline assessments should be performed within 21 days prior to the first dose and all known and suspected sites of disease should be assessed. The preferred method is contrast enhanced CT of the chest, abdomen and pelvis. A baseline MRI of the brain should be done for patients with a history or clinical symptoms of brain metastases. MRI can be used as an alternative method to CT scan if the patient has a clinical contraindication for iodine-based IV contrast or to better assess the disease. CT head scan can be used as an alternative to MRI of the brain if IV gadolinium is contraindicated.

All scans will be reviewed by an experienced radiologist trained in the study requirements. The scans will be read in sequence, and each review should be within 4 weeks of the scan being conducted to ensure that a confirmatory scan can be conducted as required.

Baseline scans will be assessed (and non-target/target lesions identified from the baseline scan alone) prior to the review of post baseline scans.

Where possible, the same radiologist should review the scan for both RECIST and irRC at the same time, and review all scans for the same patient.

Further details are provided in the IMM-101-015 Study Operations Manual.

Subsequent assessments should use the same imaging method as was used at baseline. At least one measurable lesion is required to be present at baseline based on the RECIST (version 1.1) definition of a measurable lesion.

Standard RECIST is used in this study for the main assessment of response to ensure comparability with published data. Immune Related Response Criteria (irRC) is also used in this study for assessment of response and may be used for the purposes of managing patients on protocol treatment and decision making for discontinuation of study therapy due to disease progression.

Assessment of response is based on scans at baseline, with the first scheduled scan at week 12 (±7 days) (cohort A) and week 6 (±7 days) (cohort B) and then at 8 weekly intervals (±7 days) thereafter on study. Beyond week 52, scans may be conducted every 12 weeks (±7 days) at the discretion of the investigator.

For each post-baseline scan, patients will be assigned one of the following categories:

- Complete response
- Partial response
- Stable disease
- Progression

- Inevaluable for response (specify reasons)

If imaging shows a complete response (CR) or partial response (PR), tumour imaging should be repeated at least 4 weeks later to confirm response, per RECIST 1.1 recommendations. Once a response is confirmed, repeat scans are not required to confirm subsequent instances of the same response. Patients will then return to regular scheduled imaging every 8 weeks relative to the Week 12 scan (Cohort A) or Week 6 scan (Cohort B) and 12 weekly for patients still on study after Week 52. Patients who obtain a confirmation scan do not need to undergo scheduled imaging assessment 4 weeks later (e.g., if a patient obtains a scan at Week 16 to confirm a Week 12 response, their next scheduled scan would not be performed until Week 28, with no scan at Week 20).

If imaging shows PD, it is at the discretion of the Investigator whether to keep a patient on study treatment or to stop study treatment until imaging is repeated approximately 4 weeks later in order to confirm PD, per irRC recommendations.

Confirmatory scans for responses by irRC may be carried out at the discretion of the Investigator to assist in managing treatment on study.

For all scans, assessments per RECIST 1.1 and irRC will be recorded in the eCRF.

It is recognised that some patients with advanced melanoma can have a transient tumour flare in the first few months after start of immunotherapy with subsequent disease response and this may be borne in mind when considering any early progression on study. The decision will be based on clinical judgment but to continue treatment on study after disease progression is identified by a scan, the patient should have:

- Absence of clinical symptoms and signs indicating disease progression (including worsening of laboratory values)
- No decline in performance status
- Absence of disease symptoms indicative of requiring alternative treatment
- No clinically relevant adverse effects related to study treatment

Patients in Cohort B of the study who have progression on study with IMM-101 + nivolumab treatment have the option to change on study to treatment with IMM-101 + ipilimumab, at the Investigator's discretion (see Section 7.5).

Any patients who discontinue study treatment for reasons other than progression and for whom no further treatment is deemed appropriate or desired, should remain on study and have scheduled scans until documented progression.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1 PATIENT INCLUSION CRITERIA

A patient must meet all of the following criteria to be eligible to participate in this study:

1. Patient must have a histologically-confirmed diagnosis of advanced (unresectable Stage III) or metastatic (Stage IV) melanoma excluding uveal/ocular melanoma. Patients with unknown primary melanoma are eligible
2. Patient has at least one measurable lesion by CT or MRI, according to RECIST 1.1.
3. Patient must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing during the Screening Period.

4. Patients who have had prior radiotherapy must have been completed this at least 2 weeks prior to study drug administration (Week 0, Visit 1). Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to enrolment (Week 0, Visit 1), and all related adverse events have resolved or stabilised.
5. Patient is considered suitable for treatment with nivolumab.
6. Patient provides signed informed consent for participation in the study.
7. Patient has an Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) Performance Status of ≤1 at Day 0.
8. Patient has Screening laboratory values meeting the following criteria. These should be obtained within 14 days prior to first dose on study:
   - Haemoglobin (Hb) ≥9.0g/dL, absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L and White Blood Cells (WBC) ≥ 2.0 x 10^9/L (blood transfusion to achieve these levels are not permitted within 2 weeks of this assessment)
   - Total bilirubin ≤1.5 x upper limit of normal (ULN), excluding cases where elevated bilirubin can be attributed to Gilbert's Syndrome
   - Aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and alanine transaminase (ALT; serum glutamate pyruvate transaminase [SGPT]) each ≤2.5 x ULN or ≤5 x ULN in presence of liver metastases
   - Creatinine ≤1.5 x ULN
   - Serum albumin ≥30g/L
9. Patient is aged ≥18 years.

For cohort A, the following inclusion criteria must also be met for a patient to be eligible to participate in this study:

1. Patient is treatment-naive (i.e., no prior systemic anticancer therapy for unresectable or metastatic melanoma).
2. Patient must have a tumour sample (archived tissue in the last 3 months or newly obtained biopsy) that is adequate for PD-L1 assessment prior to enrolment. Patients will be eligible to participate regardless of the level of PD-L1 expression. Patients with an inadequate archived sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo one further re-biopsy at the discretion of the investigator.

For cohort B, the following inclusion criteria must also be met for a patient to be eligible to participate in this study:

1. Patient is either currently on (or has previously received) treatment with an anti-PD-1 therapy (monotherapy or in combination) for advanced melanoma and has progressive disease by RECIST 1.1 after at least 3 doses of anti-PD-1 given as monotherapy or at least 2 doses of anti-PD-1 given in combination regimes, and has not received any therapy since for advanced melanoma. The last dose of PD-1 targeted therapy must have been received no more than 12 weeks prior to the start of Screening but more than 6 weeks prior to first IMM-101 administration. For all patients in cohort B, progression must have occurred during the PD-1 targeted treatment and the investigator must have deemed it appropriate to continue/start treatment with nivolumab beyond disease progression.

2. Patients must have recovered from any AEs related to prior anti-PD-1 containing regime to Grade 1 or have resolved.
3. Patients with a BRAF mutation must have taken at least one BRAF- and/or MEK-targeted therapy, unless patients are not candidates for, or have refused, these therapies. Anti-PD-1 therapy must be the current or last treatment for advanced melanoma prior to study entry.

6.2 PATIENT EXCLUSION CRITERIA

A patient meeting any of the following criteria is not eligible to participate in this study:

1. Patient has uveal/ocular melanoma.
2. Patient has active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible for cohort B of the study only, if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 21 days prior to first dose of study treatment.
3. Patient has previously received treatment with IMM-101.
4. Patient is either receiving concomitant treatment with another investigational product or has received such treatment within the 3 weeks prior to first IMM-101 administration.
5. Patient has any serious or uncontrolled medical disorder or co-existing active infection that, in the opinion of the Investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate.
6. Patient has any previous or concurrent malignancy. Patients will not be excluded if they have had 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 previously experienced an allergic reaction to any mycobacterial product or any monoclonal antibody.
8. Patient has a history of non-infectious pneumonitis that required steroids or current pneumonitis.
9. Patient has documented history of clinically severe autoimmune disease or a syndrome that requires systemic steroids or immunosuppressive agents.
10. Patient has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
11. Patient has a known history of or is positive for Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA [qualitative] is detected).
12. Patient has received live vaccine within 30 days before Week 0, Visit 1.
13. Patient is pregnant or breast-feeding. Female patients with reproductive potential must have a negative serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) within 72 hours prior to first administration of study drug. 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.
14. Patient has used depot corticosteroids in the 6 weeks before initiation of Screening (signing of the informed consent form [ICF]).

15. Patient has a condition requiring systemic treatment with either corticosteroids (>10mg daily prednisone equivalent) or immunosuppressant drugs (e.g., azathioprine, tacrolimus, cyclosporin) within the 14-day period before the first administration of IMM-101. Inhaled or topical steroids, and adrenal replacement steroid doses >10mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
16. Patient has received a blood transfusion within 4 weeks prior to initiation of Screening.
17. In the opinion of the Investigator, the patient is unable or unwilling to comply with the protocol.

For cohort A, patients meeting any of the following criteria are also ineligible to participate in this study:

1. Patient has received prior therapy with an anti-programmed cell death-1 (anti-PD-1), anti-PD ligand-1 (PD-L1), anti-PD-L2, anti-CD137 antibody, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agent.

For cohort B, patients meeting any of the following criteria are also ineligible to participate in this study:

1. Patient has previously experienced an AE related to anti-PD-1 therapy which, in the investigator's opinion, makes them unsuitable for further treatment with nivolumab.

6.3 PATIENT WITHDRAWAL FROM STUDY

The patient will be advised in the ICF that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or the Sponsor's discretion at any time. Reasons why the Sponsor may terminate the study are presented in Section 18.7.2.

The following are reasons for patient withdrawal:

- Any clinical adverse event (AE) or laboratory abnormality which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Withdrawn by Investigator or Sponsor due to non-compliance with the Protocol or for administrative and/or other safety reasons.
- Disease progression. Patients in the study may continue on study treatment after progression by RECIST 1.1 at the discretion of the Investigator as long as the patient has no clinical symptoms and signs indicating disease progression (including worsening of laboratory values), no decline in performance status, no disease symptoms indicative of requiring alternative treatment and no clinically relevant adverse effects related to study treatment. Patients in Cohort B of the study who have progression on study with nivolumab + IMM-101 treatment have the option to change on study to treatment with ipilimumab + IMM-101, at the Investigator's discretion (see Section 7.5).
- Pregnancy.
- Patient requests to stop study treatment.
- Termination of the study by the Sponsor.

Patients who discontinue study treatment or complete the study should where possible attend an end of study visit. This visit should be within 28±7 days after the final dose of IMM-101 when all previously unresolved adverse events will also be followed up. If an end of study visit is not possible any unresolved adverse events and update on concomitant medications should be followed up by other means of contact (e.g. telephone; Section 9.5).

Patients completing or withdrawing from the study will be followed up for survival information until database lock. Any patients who discontinue study treatment for reasons other than progression, and for whom no further treatment is deemed appropriate or desired, should remain on study and have scheduled scans until documented progression.

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 post study completion or in the event of withdrawal from the study. This data will be collected until database lock.

6.4 PATIENT FOLLOW-UP

Patients completing or withdrawing from the study will be followed up for information on survival and any subsequent therapy received until database lock. Any patients who discontinue study treatment for reasons other than progression and for whom no further treatment is deemed appropriate or desired, should remain on study and have scheduled scans until documented progression.

6.5 CONCOMITANT MEDICATIONS

6.5.1 Prohibited Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during this study. If there is a clinical indication for a medication or vaccination specifically prohibited during this study, discontinuation from study therapy may be required, with the decision to continue the patient on the study being made by the mutual agreement of the Investigator, the Sponsor and the patient.

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunosuppressive agents, except for acute treatment of potential immune-related AEs during the study
- Systemic corticosteroids >10 mg daily prednisolone equivalent, unless for acute treatment of potential immune-related AEs during the study. Systemic corticosteroids ≤10 mg daily prednisolone equivalent for more than 2 weeks are also prohibited
- Other investigational agents
- Radiation therapy apart from to a symptomatic solitary lesion which may be allowed at the discretion of the Investigator and after consultation with the Sponsor. Such therapy is only allowable after the first scheduled tumour assessment on study, unless otherwise agreed with the Sponsor
- Live vaccines within 30 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine

In addition, cytokines (e.g., Interferon alpha [IFN-α]), monoclonal antibodies, anti-tumour vaccines, and biological response modifiers should be used with caution when given concomitantly with IMM-101.

Any prior and concomitant therapy/medications taken up to 30 days before the first dose of study medication will be recorded in the patient's eCRF at Screening.

6.5.2 Acceptable Concomitant Medications

Any other medication not listed in section 6.5.1 that is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of IMM-101 may be given at the discretion of the Investigator.

Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) may be used. Short courses of corticosteroids (≤10 mg daily prednisolone equivalent for up to 2 weeks) for prophylaxis or for treatment of non-autoimmune conditions is permitted.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids and including changes in drug dosage, frequency, and administration route.

All concomitant medications received within 30 days before the first dose of study medication and up to and including 30 days after the last dose of study medication should be recorded.

6.5.3 Concomitant Procedures

Any diagnostic, therapeutic, or surgical procedures performed during the trial will be recorded in the eCRF, including the date and reason for the procedure.

6.5.4 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in patients on study after consultation with the Medical Monitor. Any such resections should follow confirmation of tumour shrinkage by CT or MRI scan and, preferably, after a subsequent scan indicates no further shrinkage. Patients with a PR who go on to have surgical resection of remaining disease will be considered a PR.

6.6 PREGNANCY

All patients who are not either surgically sterilised, postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 18 months without an alternative medical cause will be considered postmenopausal), or not heterosexually active for the duration of the study must be instructed to use adequate, effective contraception whilst taking part in the study and for at least 6 months after discontinuation of treatment.

Acceptable adequate, 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. True abstinence is allowable for prevention of pregnancy but any women of child-bearing potential who choose this method must continue to have pregnancy tests.

In the event of a pregnancy, whenever possible, consent should be obtained for it to be followed to term, any premature terminations reported to Bionical-Emas, and the status of the mother and child should be reported to the Sponsor after delivery and at important developmental milestones during the first year.

6.6.1 Female Patient's Pregnancy

Patients who become pregnant during the study must be withdrawn from the study immediately.

Patients must be instructed to notify the Investigator if it is determined after completion of (or withdrawal from) the study that they became pregnant during the study within 6 months of last dose on study.

6.6.2 Male Patient's Partner's Pregnancy

Male patients must be instructed to notify the Investigator if it is determined that, during the study or after completion of the study, their partner became pregnant during the study.

6.7 WITHDRAWAL OF CONSENT

Patients who request to discontinue study treatment can remain in the study and continue to be followed for protocol specified follow-up procedures unless the patient wishes to withdraw from study procedures as well as from study treatment. If a patient should wish to withdraw consent for future follow-up (as in Section 6.4) they should notify the Investigator of this decision. The withdrawal of consent should be explained in the medical records by the Investigator, to confirm whether the withdrawal is from further treatment with study drug only, or also from study procedures and/or post treatment study follow-up, and entered on the appropriate eCRF page.

6.8 FURTHER TREATMENT AFTER THE END OF THE STUDY

For patients who leave the study, either due to early withdrawal or completion, normal standard of care (SOC), according to local practice, will continue as necessary.

7. STUDY TREATMENT

7.1 INVESTIGATIONAL PRODUCT

7.1.1 Manufacture and Formulation

IMM-101 is formulated at a concentration of 10 mg/mL in borate buffered saline, pH 7.7−8.3. It is supplied in a variety of single use vials containing up to 2.0 mL. The dose volume is 0.1 mL given intradermally over the deltoid muscle. The product is particulate and must be shaken gently before use to re-suspend the particulate matter. It should be stored upright at 2°C to 8°C and protected from light.

Primary manufacture is undertaken to GMP standards at BioElpida, Saint Priest, France. Formulation of drug product and aseptic filling is carried out by Nova Laboratories, Leicester, UK. Rigorous in-process control testing and final product testing against pre-defined specifications provide assurance of the quality of IMM-101.

The batch(es) to be used in this study are comparable to those previously tested in pre-clinical safety studies and the previous Phase 1 and 2 studies.

Batch number(s) and expiry date(s) will be documented, including in the Sponsor File and in the final clinical study report.

7.1.2 Packaging and Labelling

IMM-101 will be labelled in local language. The label will contain the information as required by Annex 13 of the GMP guidelines of the European Commission, ICH-GCP guidelines, and other prevailing legislation.

7.1.3 Storage

IMM-101 supplied by the Sponsor is to be used exclusively in the clinical study according to the instructions of this protocol.

The product must be stored in a refrigerator at 2°C to 8°C and protected from light. After the product has been removed from the refrigerator it must be allowed to equilibrate at ambient temperature for 5 to 10 minutes before being used. The product must be used within 6 hours of being removed from the refrigerator or it should be discarded.

IMM-101 must be stored in securely locked areas not generally accessible until administered to the patients. The key to the storage area is to be kept by the Investigator (or delegated person responsible for the study drug). The store will be accessible only to those persons authorised by the Investigator to dispense/administer IMM-101.

Further details on drug handling will be provided in a separate operations manual.

7.1.4 Destruction of Surplus Medication

All surplus IMM-101 will be sent for destruction following authorisation from the Sponsor and the destruction documented.

7.1.5 Investigational Product Accountability

The Investigator, or an approved representative, must maintain records of the product's delivery to the study site, the inventory at the site, the use for each patient, and will ensure that all investigational products are stored in a secure, limited access area. These records must include dates, quantities, batch/serial numbers, expiry dates, and the unique code numbers assigned to the investigational product(s) and study patients. A temperature log of the medication storage refrigerator must also be kept. Investigators must maintain records that document adequately that the patients were provided with the doses specified by the Protocol and reconcile all investigational product received from the Sponsor.

To ensure adequate records, IMM-101 will be accounted for on an on-going basis throughout the study in drug accountability forms at the study site. Records will be kept in accordance with the applicable regulatory requirements and the Investigator will ensure that IMM-101 is dispensed only by qualified site staff. These records will be independently monitored by a study monitor.

7.1.6 Dosing

IMM-101 is administered as a single 0.1 mL intradermal injection of IMM-101 (10 mg/mL) into the skin overlying the deltoid muscle, with the arm being alternated between each dose. The Investigator will have been appropriately trained *a priori* in the technique of intradermal injection.

Previous clinical experience with IMM-101 has suggested that this dose is well tolerated. The skin reaction that develops at the site of injection is characterised by erythema, local swelling and occasionally mild ulceration. All symptoms are to be expected given the known pharmacology of the product and previous clinical experience. Furthermore, data from safety

and tolerability studies with IMM-101 have revealed that skin reactions resolve satisfactorily over time and do not impair daily activity.

The first dose of IMM-101 administered to each patient in the study is followed by vital signs monitoring for at least 2 hours under medical supervision with resuscitation facilities available as a precautionary measure.

The treatment regimen will be 1 dose of IMM-101 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 with a window of +/- 2 days allowed.

Nivolumab and ipilimumab are administered according to the prescribing information. When either nivolumab or ipilimumab are administered on the same day as IMM-101, according to the Schedule of Assessments, patients will receive IMM-101 first. The first dose of nivolumab administered to each patient on study is given at least 2 hours after the first dose of IMM-101.

The Study Schedule of Assessments is presented in Appendix 1.

7.2 DOSE ADJUSTMENT CRITERIA

7.2.1 Dosing delays

The prescribing information for nivolumab and for ipilimumab should be referred to for reasons for withholding or permanently discontinuing these medications. When a dose delay or treatment discontinuation is indicated for nivolumab or ipilimumab based on adverse events, IMM-101 should also be withheld/discontinued in the same manner and the reason for the dose delay recorded in the eCRF. Dosing delays should be applied for any other adverse events considered related to any study drug with the related study treatment(s) withheld until treatment can resume. Dosing delay can also apply to any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication(s).

In the event of any immune-mediated adverse reactions of ≥ Grade 3 (severe), IMM-101 and nivolumab (or ipilimumab when used for cohort B) should be withdrawn, either until resolution of the event or permanently, at the discretion of the Investigator. Treatment delays due to Grade 2 immune-related adverse reactions will be assessed on a case-by-case basis by the Investigator.

Permanent discontinuation should be considered for any severe or life-threatening adverse reactions, with the final decision on whether to stop treatment made after discussion with the Sponsor.

Ideally, the nivolumab dosing regimen chosen at the start of the study should be maintained (notwithstanding modifications due to AEs as described above). However, if a 480mg 4-weekly nivolumab dosing is not tolerated, the patient may be switched to a 240mg 2 weekly regimen.

The dose of ipilimumab should not be modified for any reason.

The dose of IMM-101 may be reduced in cases of injection site reactions (see Section 7.2.3).

7.2.2 Resumption of Dosing

Patients may resume treatment with study drugs when the drug-related AE(s) resolve to Grade ≤1 or baseline value. In cases where the toxicity does not resolve or improve to ≤Grade 1 within 12 weeks after last administration of study drug, discontinuation from study therapy should be considered after discussion with the Sponsor.

Patients still at Grade 2 may continue in the study only if asymptomatic and controlled, at the Investigator's discretion. However, drug-related pulmonary toxicity, diarrhoea, or colitis, must have resolved to baseline before treatment is resumed.

When treatment is restarted, the patient should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past this point, the next scheduled time point will be delayed until dosing resumes.

Two dosing delays due to the same toxicity will be permitted. In the event of a third occurrence of the same toxicity which would require dosing delay, all study therapy will be discontinued permanently.

7.2.3 IMM-101 Injection Site Reactions

Injection site reactions are expected and therefore it is important not to withhold IMM-101 in these situations, but to continue at a lower dose and/or with dose interval adjustments. IMM-101 should only be withheld if felt to be necessary by the Investigator and/or patient due to intolerable injection site reactions.

During the study, at the discretion of the Investigator, the dose interval may be modified provided the minimum period between doses is at least 12 days (14±2 days) between visits 1-2, 2-3, 5-6 and 6-7. The 28 day interval ±2 days between other doses (3-5, 7-9 and all after this point) should be maintained, subject to skin reactions or other reasons as detailed above (7.2.1). Administration of nivolumab and, if used in cohort B, for ipilimumab, should continue according to the normal schedule irrespective of any dosing delays for IMM-101 due to injection site reactions.

In the event of an injection site reaction of ≥Grade 3 (severe) as measured by the NCI CTCAE v4.0, 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) 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 4 weeks.

Any change in the dose of IMM-101 or the frequency at which it is administered must be recorded in the patient's eCRF.

7.3 PERMANENT DISCONTINUATION OF STUDY TREATMENT FOR PATIENTS

The prescribing information for nivolumab and for ipilimumab should be referred to for reasons for permanently discontinuing these medications. When treatment discontinuation is indicated for nivolumab or ipilimumab based on adverse events, IMM-101 should also be discontinued. In the event of any immune-mediated adverse reactions of ≥Grade 3 (severe), IMM-101 and nivolumab (or ipilimumab when used for cohort B) should be withdrawn, either until resolution of the event or permanently, at the discretion of the investigator.

Permanent discontinuation for a patient should be considered for any severe or life-threatening adverse reactions, with the final decision on whether to stop treatment made after discussion with the Sponsor.

A dosing delay due to an adverse event failing to resolve or improve to ≤Grade 1 within 12 weeks after last administration of study drug, may result in discontinuation of a patient from study therapy, at the Investigator's discretion and after discussion with the Sponsor. Two dosing delays due to the same toxicity are permitted on study but a third occurrence of the same toxicity which would require dosing delay, will result in permanent discontinuation of the patient from the study. Patients discontinuing the study will be followed up as in Section 6.4.

7.4 DURATION OF DOSING

Dosing with IMM-101 is allowed up to a maximum of 18 months for all patients on study in both cohorts A and B. Treatment for patients in both cohorts may stop before the 18 month maximum due to disease progression as assessed by RECIST 1.1 (subject to the qualifications described in 7.5), unacceptable side-effects, the Investigator's or patient's decision to discontinue treatment or other reasons as specified in Section 6.3. Patients with a complete response maintained over 2 scans should continue treatment unless the Investigator considers this not in the patient's best interest.

7.5 TREATMENT BEYOND PROGRESSION

Patients in cohorts A and B who have documented disease progression by RECIST 1.1 may continue treatment with IMM-101 + nivolumab on study if they have a clinical benefit and no decline in performance status, no clinically relevant adverse effects with the study treatment as determined by the investigator, or are not deemed to require alternative treatment (See Section 6.3).

Patients in cohort B who fail to respond to treatment with IMM-101 + nivolumab i.e., they have either documented progression by RECIST 1.1, or clinical progression (but without meeting the RECIST 1.1 rules for progressive disease), and, in both cases have no prior recorded response, have the option to change treatment on study to ipilimumab + IMM-101 if the Investigator considers this in the patient's best interest and the patient has not previously received ipilimumab off study (monotherapy or in combination). This treatment may continue until the maximum 4 doses of ipilimumab have been received or stop sooner due to unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of study treatment, whichever is the sooner. Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner.

7.6 NON-INVESTIGATIONAL PRODUCTS

7.6.1 Nivolumab

According to Investigator choice, Nivolumab will be given as 3mg/kg IV infusion every two weeks, 240mg IV infusion every two weeks or 480mg IV infusion every four weeks, in accordance with the prescribing information.

Ideally, the nivolumab dosing regimen chosen at the start of the study should be maintained (notwithstanding modifications due to AEs as described above). However, if a 480mg 4-weekly nivolumab dosing is not tolerable, then the patient may be switched to a 240mg 2-weekly regimen. The reason for nivolumab dosing modification will be recorded in the eCRF.

In instances when nivolumab and IMM-101 are given on the same day, IMM-101 will be administered first. The first dose of nivolumab administered to each patient on study is given at least 2 hours after the first dose of IMM-101.

In the event of toxicity, doses may be delayed (see section 7.2.1).

For patients completing the study, the last dose of nivolumab is given at Week 76 or 78 (dependent on 2 weekly or 4 weekly dosing regimen). Any patients in Cohort A who are to

continue to receive nivolumab off study should have their End of Study visit before any such off-study treatment.

7.6.2 Ipilimumab

If used on study for patients in cohort B, ipilimumab is to be administered as a 3 mg/kg IV infusion over 90 minutes every three weeks for a maximum of 4 doses, in accordance with the prescribing information. The first dose of ipilimumab can start at any time during the study but must be at least 2 weeks after the last dose of nivolumab. In instances when ipilimumab and IMM-101 are given on the same day, IMM-101 will be administered first.

In the event of toxicity, doses may be delayed (see section 7.2.1), but all ipilimumab doses must be administered within 16 weeks of the first dose.

Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner.

7.7 TREATMENT COMPLIANCE

Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF. Details of each IMM-101 administration (including date and time of the injection, dose and site of administration) will be recorded in the patient's eCRF, along with any missed doses. Compliance for nivolumab and ipilimumab (where used in cohort B) will also be monitored and details of dosing recorded in the eCRF.

7.8 RANDOMISATION, BLINDING AND PATIENT NUMBERING

This is an open-label, non-randomised study and as such no randomisation or unblinding procedures are required. Each patient at each centre will be allocated a unique number at Screening.

Once a unique patient identifier has been assigned, no attempt should be made to use that number again within the centre if, for example, a patient is withdrawn from the study. No patient should be entered into the study more than once and patients withdrawn during the course of the study will not be replaced. If a patient number is allocated incorrectly, the Study Monitor must be notified as soon as the error is discovered, to agree what action should be taken.

8. STUDY PROCEDURES AND SCHEDULE

8.1 STUDY PROCEDURES: SCREENING AND ENROLMENT (DAY -21 TO DAY -1)

The Study Schedule of Assessments for the Screening visit is provided in Appendix 1.

Patients will complete the Screening assessments within 21 days of enrolment, to establish their eligibility to participate. Written, dated informed consent will be obtained from the patient before any study-specific activities are performed.

The patient's GP will be informed in writing about the participation of his/her patient in the study. A record will be kept of patients who undergo the pre-treatment Screening but who do not enrol into the study in a "Patient Screening Log".

The following procedures and assessments will be conducted during the Screening Phase and recorded in the patient's electronic case report form (eCRF):

- Informed consent
- Patient eligibility (inclusion/exclusion criteria; see Section 6.1, 6.2)
- Demographics and baseline data (gender, date of birth, ethnicity and height)
- Complete medical history including disease history and treatment, any history of autoimmune conditions (see exclusion criterion 11), any concurrent illnesses and history of previous vaccinations (e.g. Bacille Calmette-Guérin [BCG], smallpox, yellow fever)
- Complete physical examination including assessment of injections that were received in the 6 months prior to Screening, and pre-existing injection site reactions (i.e. BCG or prior cancer treatment reactions) (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood and urine samples for safety laboratory assessment (see Section 8.4.7)
- Document results and record date of last computerised tomography/magnetic resonance imaging (CT/MRI) scan. If no scan has been performed in the 21 days prior to Visit 1 a scan should be performed (see Section 8.5.2)
- Serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) if applicable. This must be within 72 hours prior to first dose of study drug (IMM-101). Both male and female patients should be instructed to use adequate, effective contraception whilst taking part in the study and for at least 6 months after discontinuation of treatment (see Section 8.4.8)
- Blood sample for Hepatitis B and C test (see Section 8.4.7)
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status. 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 (see Section 8.4.4)
- 12-lead electrocardiogram (ECG; see Section 8.4.6)
- Biopsy for PD-L1 assessment (*Cohort A only*, see Section 8.5.4.1; not applicable if an adequate tissue sample archived in the preceding 3 months is available)
- BRAF testing
- Blood sample for immunological marker assessment (see Section 8.5.4.2)
- Biopsy sample for immunological marker assessment (see Section 8.5.4.1). For patients in Cohort A, this is the same sample as used for PD-L1 assessment.
- Record any prior/concomitant therapy (including radiotherapy and surgery) and procedures taken up to 30 days before the first dose of study medication (see Section 6.5)

- AE/serious adverse event (SAE) reporting from the time of signing informed consent (see Section 9.2/9.3).

8.2 STUDY PROCEDURES: TREATMENT PHASE

The Study Schedule of Assessments for the Treatment Phase is provided in Appendix 1.

The following procedures and assessments will be conducted during the Treatment Phase and recorded in the patient's eCRF:

Week 0 (Visit 1)

This visit should take place as soon as possible after eligibility is confirmed; the following procedures will be carried out before administration of the first dose of IMM-101 on study.

- Re-check the patient's eligibility (i.e., inclusion and exclusion criteria) including a review of blood and serum samples
- Measure and record vital signs (resting blood pressure, pulse, body temperature, and weight). (see Section 8.4.5)
- ECOG/WHO performance status (see Section 8.4.4)
- Record any concomitant medications/procedures since the previous visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- If more than 7 days since the screening assessment, the following should also be carried out:
    - Physical Examination (see Section 8.4.2)
    - Blood sample for safety laboratory assessment (see Section 8.4.7)

Note: all eligibility assessments may be carried out one day before the scheduled day of dosing (visit day).

When eligibility has been confirmed:

- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)
- Patients should be followed by vital sign monitoring for at least 2 hours after first administration of IMM-101 under medical supervision with resuscitation facilities available as a precautionary measure, prior to leaving the study site (see Section 7.1.6).

Week 2 (Visit 2), Week 10 (Visit 6) both ±2 days

- Physical examination (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood samples for safety laboratory assessment (see Section 8.4.7).
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)

- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed.

Week 4 (Visit 3), Week 8 (Visit 5), Week 40 (Visit 21), – all visits ±2 days

- Physical examination (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.4.4)
- Blood sample for immunological marker assessment (*Cohort A only* see Section 8.5.4.2)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed.

Week 6 (Visit 4) ±2 days

- CT/MRI scan (*Cohort B only,* ±7 days)
- Blood sample for immunological marker assessment (*Cohort B only* see Section 8.5.4.2)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Cohort A only - if a 4 weekly nivolumab dosing regimen is chosen by the investigator, this study visit is not required unless clinically indicated.

Week 12 (Visit 7) ±2 days

- Physical examination (see Section 8.4.2)

- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- CT/MRI scan (*Cohort A only,* ±7 days) (scans can be every 12 weeks beyond Week 52 - see Section 8.5.1)
- Biopsy to be scheduled (*Cohort A only*, to be performed within 2 weeks after this visit).
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.7)
- Blood sample for immunological marker assessment (*Cohort A only* see Section 8.5.4.2,)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Week 20 (Visit 11), Week 28 (Visit 15), Week 36 (Visit 19), Week 44 (Visit 23), Week 52 (Visit 27), – all visits ±2 days

- Physical examination (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- CT/MRI scan (*Cohort A only,* ±7 days) (scans can be every 12 weeks beyond Week 52 - see Section 8.5.1)
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.4.4)
- Blood sample for immunological marker assessment (*Cohort A only,* see Section 8.5.4.2)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Week 14 (Visit 8), Week 22 (Visit 12), Week 30 (Visit 16), Week 38 (Visit 20), Week 46 (Visit 24) – all visits ±2 days

- CT/MRI scan (*Cohort B only,* ±7 days) (scans can be every 12 weeks beyond Week 52 - see Section 8.5.1). Record any concomitant medications since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- Blood sample for immunological marker assessment (*Cohort B only,* see Section 8.5.4.2)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Cohort A only - if a 4 weekly nivolumab dosing regimen is chosen by the investigator, this study visit is not required unless clinically indicated.

Week 18 (Visit 10), Week 26 (Visit 14), Week 34 (Visit 18), Week 42 (Visit 22), Week 50 (Visit 27), Week 58 (Visit 30), Week 66 (Visit 34), Week 74 (Visit 38) – all visits ±2 days

- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3)
- Nivolumab administration (see Section7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed.

If a 4 weekly nivolumab dosing regimen is chosen by the investigator, this study visit is not required unless clinically indicated.

Week 54 (Visit 28), Week 62 (Visit 32), Week 70 (Visit 36), Week 78 (Visit 40) - all visits ±2 days

- CT/MRI scan (*Cohort B only,* ±7 days) (scans can be every 12 weeks beyond Week 52 - see Section 8.5.1)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Cohort A only - if a 4 weekly nivolumab dosing regimen is chosen by the investigator, this study visit is not required unless clinically indicated.

Week 16 (Visit 9), Week 24 (Visit 13), Week 32 (Visit 17), Week 48 (Visit 25), Week 56 (Visit 29), Week 64 (Visit 33), Week 72 (Visit 37) - all visits ±2 days

- Physical examination (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.4.4)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed.

Week 60 (Visit 31), Week 68 (Visit 35), Week 76 (Visit 39) - all visits ±2 days

- Physical examination (see Section 8.4.2)
- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- CT/MRI scan (*Cohort A only,* ±7 days) (scans can be every 12 weeks beyond Week 52 - see Section 8.5.1)
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.4.4)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3; all SAEs to be reported within 24 hours)
- Solicited and visible injection site reactions (see Section 8.4.10)
- IMM-101 administration by intradermal injection (see Section 7.1.6)
- Nivolumab administration (see Section 7.6.1)

Note: all assessments may be carried out one day before the scheduled visit when dosing is performed. For CT/MRI scan, the specified window applies.

Ipilimumab Administration (*Cohort B patients only*)

The Study Schedule of Assessments for ipilimumab is provided in Appendix 1 and further details on ipilimumab administration are given in Section 7.6.2.

Patients in cohort B who have progression on study (either by RECIST 1.1 or clinical progression, see Section 7.5), have the option to change treatment on study to IMM-101 + ipilimumab if the Investigator considers this in the patient's best interest. This treatment may continue until the maximum 4 doses of ipilimumab have been received or stop sooner due to

unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of study treatment, whichever is the sooner.

Patients receiving ipilimumab on study will continue to follow the usual assessments, as listed in Section 8.2 above, but may have additional visits to receive ipilimumab when AE/SAE and concomitant medications/procedures will always be checked for and reported, as in the Additional Schedule in Appendix 1.

Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner (see Section 7.5)

8.3 STUDY PROCEDURES: WITHDRAWAL/END OF STUDY VISIT (WEEK 80)

The Study Schedule of Assessments for the Withdrawal/EOS visit is provided in Appendix 1.

When a patient withdraws from or completes the study, where possible the patient should attend an EOS visit. This visit should be within 28±7 days after the final study dose of IMM-101. If an end of study visit is not possible, any unresolved adverse events and update on concomitant medications should be followed up by other means of contact (e.g. telephone; Section 9.5).

The following assessments will be performed: Physical examination (see Section 8.4.2)

- Vital signs (resting blood pressure, pulse, body temperature, and weight; see Section 8.4.5)
- Blood sample for safety laboratory assessment (see Section 8.4.7).
- CT/MRI scan (*only required if there is more than 8 weeks elapsed since the last scan or more than 12 weeks elapsed if last scan was after week 52 and only when there is already no documented progression*)
- Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status (see Section 8.4.4)
- 12-lead ECG (See Section 8.4.6)
- Record any concomitant medications/procedures since the last visit (see Section 6.5)
- AE/SAE reporting (see Section 9.2/9.3)
- Solicited and visible injection site reactions (see Section 8.4.10)

For patients completing the study, the last dose of nivolumab is given at Week 76 or 78 (dependent on 2 weekly or 4 weekly dosing regimen). Any patients in Cohort A who are to continue to receive nivolumab off study should have their End of Study visit before any such off-study treatment.

In addition, after patients withdraw from the study, their GP will be contacted for continued collection of survival data and information on subsequent therapy (see Section 6.3).

8.4 SAFETY MEASUREMENTS

The following safety evaluations will be performed at Screening and during the Treatment Phase of the study:

- Medical history to capture underlying conditions
- Physical examinations
- Evaluation of AEs at post-screening visits
- ECOG/WHO performance status
- Vital signs and weight
- Laboratory tests: haematology, clinical chemistry, urinalysis (Screening only), pregnancy test (at screening and during study when clinically indicated), thyroid function, hepatitis B/C testing (Screening only).
- Concomitant medications/procedures (prior medications at screening)
- Injection site reactions

8.4.1 Medical History

The Investigator or qualified designee will obtain the patient's medical history at the Screening visit. Medical history will include all active conditions, and any conditions diagnosed within the preceding 5 years that are considered to be clinically significant by the Investigator.

8.4.2 Physical Examination

A full physical examination, including assessment of injections received prior to Screening, and pre-existing injection site reactions (i.e. BCG or prior cancer treatment reactions), will be performed at Screening, at every visit where IMM-101 is administered and at the EOS visit.

Additional physical examinations to those scheduled will be performed as per the Investigator's routine procedures.

8.4.3 Adverse Events

All AEs will be recorded on the patient's eCRF from the time of informed consent. All AEs will be followed until resolution, death, or 30 days after the last administration of study treatment (whichever comes first). See section 9.2 for further information on the recording of AEs.

8.4.4 ECOG/WHO Performance Status Assessment

To be eligible for entry into this study, patients must have an ECOG/WHO Performance Status of ≤1 at Week 0, Visit 1. Two observers are required to assess performance status at the Screening and Week 0, Visit 1 assessments. If there is any discrepancy between the two scores, the highest (worst) assessment will be used. Subsequent assessments are at Week 4 and every 4 weeks thereafter on study and only require one assessor. The assessment guidelines are provided in Appendix 2[24].

8.4.5 Vital Signs and Weight

Vitals signs (resting blood pressure, pulse, and body temperature) and weight will be measured and recorded in the patient's eCRF at Screening, at every visit where IMM-101 is administered and at the EOS visit.

Patients will be followed by vital sign monitoring for at least 2 hours after administration of the first dose of IMM-101 with monitoring every 15 minutes during this period, under medical supervision with resuscitation facilities available as a precautionary measure.

Additional measures of vital signs to those scheduled in this study will be performed as per the Investigator's routine procedures.

8.4.6 Electrocardiogram

12-lead ECG measures will be recorded at Screening and at the EOS visit. Additional 12-lead ECG measures to those scheduled in this study may be performed as per the Investigator's routine procedures. The results will be reviewed by the Investigator and recorded in the patient's eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. A description should be given for any clinically significant abnormality. The QT interval corrected using Fridericia's factor will be recorded.

8.4.7 Laboratory Evaluation

Laboratory safety tests (e.g., complete blood count (CBC), clinical chemistries, and thyroid function), will be assessed at designated intervals throughout the study according to Table 1 (see also Appendix 1).

Table 1: Study Timelines for Laboratory Samples

Timeline	Measure	Volume[1]
Screening (Day -21 to -1)	Serum pregnancy test. Hepatitis B/C test Safety blood analysis: CBC with differential, clinical chemistry including ALT, ALP, AST, bilirubin (total, direct), albumin, lipase, amylase, GGT, LDH, urea, electrolytes, creatinine, urea, glucose, TSH, free T4, free T3 Urinalysis	10 mL blood
Treatment Phase[3] **Visit 1 (Week 0)[2]** **Visit 2 (Week 2)** **Visit 3 (Week 4)** **Visit 5 (Week 8)** **Visit 6 (Week 10)** **Visit 7 (Week 12)** **Visit 9 (Week 16)** **Visit 11 (Week 20)** **Visit 13 (Week 24)** **Visit 15 (Week 28)** **Visit 17 (Week 32)** **Visit 19 (Week 36)** **Visit 21 (Week 40)** **Visit 23 (Week 44)** **Visit 25 (Week 48)** **Visit 27 (Week 52)** **Visit 29 (Week 56)** **Visit 31 (Week 60)** **Visit 33 (Week 64)** **Visit 35 (Week 68)** **Visit 37 (Week 72)** **Visit 39 (Week 76)**	Serum pregnancy test (as required) Safety blood analysis: CBC with differential, clinical chemistry including ALT, ALP, AST, bilirubin (total, direct), albumin, lipase, amylase, GGT, LDH, urea, electrolytes, creatinine, urea, glucose, TSH, free T4, free T3	
Withdrawal/EOS Visit	Safety blood analysis: CBC with differential, clinical chemistry including ALT, ALP, AST, bilirubin (total, direct), albumin, lipase, amylase, GGT, LDH, urea, electrolytes, creatinine, urea, glucose, TSH, free T4, free T3	10 mL blood

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; CBC: complete blood count; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase.

[1] **The maximum volume of blood collected per patient at a single visit specifically for the safety endpoints will not exceed 10 mL** Blood samples for immunomarker analyses are provided in Section 9.6

[2] **Only to be repeated if more than 7 days between screening test and commencing any study treatment (Visit 1)**

[3] **Blood samples may be taken one day before the day of dosing (visit day).**

8.4.8 Pregnancy Test

A serum pregnancy test (β-hCG) will be conducted for all eligible females of child-bearing potential during Screening and at any other time during the study if pregnancy is suspected (Study Schedule of Assessments, in Appendix 1). Female patients with reproductive potential must have a negative serum pregnancy test (β-hCG) documented within 72 hours prior to the first dose of study drug.

See section 6.6 for contraception requirements on study and handling of pregnancy.

8.4.9 Concomitant Medications

See section 6.5 for information on prohibited and allowed concomitant medications.

8.4.10 Injection Site Reactions

Mild or moderate local reactions at the injection site are expected. Patients are likely to experience a skin reaction and some discomfort around the injection site.[1] Each patient will be given advice regarding the management of local injection site reactions and generalised systemic symptoms (e.g., pyrexia). Where symptoms persist or result in functional limitations, patients will be advised to attend the next possible research clinic or see their own GP.

Before each administration of IMM-101, previous injection sites must be inspected for local reaction(s). Although a formal assessment is performed before each injection, an injection site reaction may be recorded as an AE at any time if considered appropriate to do so by the Investigator.

During the study, at the discretion of the Investigator, the dose interval may be modified provided the minimum period between doses is at least 12 days (14±2 days) between visits 1-2, 2-3, 5-6 and 6-7. The 28 day interval ±2 days between other doses (3-5, 7-9 and all after this point) should be maintained, subject to skin reactions or other immune-related AEs as detailed below.

Local skin reactions are expected but in the event of an injection site reaction of ≥Grade 3 (severe) as measured by the NCI CTCAE v4.03[23], 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) 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 4 weeks.

If dosing is discontinued or the patient withdraws from the study as a result of an intolerable injection site reaction, this must be recorded in the eCRF.

8.5 EFFICACY MEASUREMENTS

The primary efficacy endpoint of the study is ORR. Response assessment based on RECIST 1.1 is used as the primary assessment of ORR and ORR based on irRC will be evaluated as a secondary assessment of the efficacy endpoints.

8.5.1 Tumour Burden

During the study, response will be assessed by CT or MRI, the same imaging method used at baseline (Screening) and during the remainder of the study for each patient. The preferred method is contrast enhanced CT of the chest, abdomen and pelvis. A baseline MRI of the brain should be done for patients with a history or clinical symptoms of brain metastases. MRI can be used as an alternative method to CT scan if the patient has a clinical contraindication for iodine-based IV contrast or to better assess the disease. CT head scan can be used as an alternative to MRI of the brain if IV gadolinium is contraindicated.

All baseline evaluations must be performed no more than 21 days before enrolment and should be as close as possible to the beginning of treatment. All known and suspected sites of disease should be assessed and at least one measurable lesion according to RECIST 1.1 criteria must be present at screening. A maximum of 5 target lesions can be recorded with a maximum of 2 lesions per organ representative of all involved organs (see Section 8.5.2.1). All measurements should be recorded in millimetres (mm). Imaging based evaluation should **always** be used

rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

All scans will be reviewed by experienced radiographers trained in the study requirements. The scans will be read in sequence, and each review should be within 4 weeks of the scan being conducted to ensure that a confirmatory scan can be conducted as required.

Baseline scans will be assessed (and non-target/target lesions identified from the baseline scan alone) prior to the review of post baseline scans.

Where possible, the same radiographer should review the scan for both RECIST 1.1 and irRC at the same time, and review all scans for the same patient.

Further details are provided in the IMM-101-015 Study Operations Manual.

Chest CT is preferred over chest x-ray, however lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter by caliper measurement. For the case of skin lesions, documentation by colour photography using a ruler to estimate the size of the lesion is possible, but CT is always preferred.

Ultrasound should not be used for lesion measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI should take place.

Endoscopy and laparoscopy should not be used for objective tumour evaluation.

Immune Related Response Criteria (irRC) is also used in this study for assessment of response and may be used for the purposes of managing patients on protocol treatment and decision making for discontinuation of study therapy due to disease progression. For the purposes of irRC, up to five lesions in a single organ may be recorded with a maximum of 10 visceral and five cutaneous index lesions (see Section 8.5.2.3). The first post-baseline radiological assessment of tumour response status will be performed at Week 12 (±7 days) for patients in cohort A and at Week 6 (±7 days) for patients in cohort B unless there is clinical indication (based on Investigator's assessment) warranting earlier imaging. Subsequent radiological assessments are at 8 weekly intervals thereafter on study. Beyond week 52, scans may be conducted every 12 weeks at the discretion of the investigator.

If imaging shows a complete response (CR) or partial response (PR), according to the rules in 8.5.3.1, tumour imaging should be repeated at least 4 weeks later to confirm response, per RECIST 1.1 recommendations. The results of both the first (original) scan showing a CR or PR according to the rules in 8.5.3.1 as well as those of the confirmatory scan should be entered into the eCRF. The values for the original scan should not be amended in the eCRF even if the confirmatory scan does not confirm the results of the original scan. The confirmed response is used for the calculation of BOR (and hence the primary endpoint of ORR). However, BOR and hence ORR, using unconfirmed responses will also be calculated for comparability with published data. Following a confirmatory scan, the patient will then return to regular scheduled imaging every 8 weeks relative to the Week 12 scan (Cohort A) or Week 6 scan (Cohort B) and 12 weekly for patients still on study after Week 52. Patients who obtain a confirmation scan do not need to undergo scheduled imaging assessment 4 weeks later (e.g., if a patient obtains a scan at Week 16 to confirm a Week 12 response, their next scheduled scan would not be performed until Week 28, with no scan at Week 20). Once a response is confirmed, repeat scans are not required to confirm subsequent instances of the same response.

If imaging shows PD, it is at the discretion of the investigator whether to continue or stop study treatment (i.e. both IMM-101 and nivolumab/ipilimumab) recognising that some patients with advanced melanoma can have a transient tumour flare in the first few months after start of immunotherapy with subsequent disease response. This decision will be based on clinical judgment but to continue treatment on study after disease progression is identified by a scan, the patient should have:

- Absence of clinical symptoms and signs indicating disease progression (including worsening of laboratory values)
- No decline in performance status
- Absence of disease symptoms indicative of requiring alternative treatment
- No clinically relevant adverse effects related to study treatment

Patients in cohort B who fail to respond to treatment with IMM-101 + nivolumab i.e., they have either documented progression by RECIST 1.1, or clinical progression (but without meeting the RECIST 1.1 rules for progressive disease), and, in both cases have no prior recorded response, have the option to change treatment on study to ipilimumab + IMM-101 if the investigator considers this in the patient's best interest and the patient has not previously received ipilimumab off study (monotherapy or in combination). Any patients who discontinue study treatment for reasons other than progression and for whom no further treatment is deemed appropriate or desired, should remain on study and have scheduled scans until documented progression.

At baseline, tumour lesions/lymph nodes will be categorised as measurable or non-measurable as follows:

8.5.1.1 Measurable Lesions

Lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size, for RECIST 1.1, of:
• 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
• 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
• 20mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be at least 15mm in short axis when assessed by CT scan. At all scans, only the short axis will be measured and followed. For irRC, bidimensional measurements are required with measurable lesions having a minimum size of 5 x 5 mm.

8.5.1.2 Non-measurable Lesions

These are all other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

8.5.1.3 Special considerations regarding lesion measurability

Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (measurable nor non-measurable).
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.5.2 Baseline Documentation of Lesions - RECIST 1.1

All target/non-target lesions must be identified from the baseline scan, prior to availability of any post baseline scans. Reassignment of target/non-target lesions following assessment and review of later scans should only be made to correct a genuine error by the radiographer and after consultation with the Sponsor. In the event of reassignment of target/non-target lesions post baseline under these circumstances, a protocol deviation shall be recorded in the eCRF including the reason for the error. In other circumstances, lesions not already identified as target/non-target lesions appearing on post-baseline scans (even if retrospectively considered to be present at baseline scan) shall be considered new post-baseline lesions only.

8.5.2.1 Target Lesions

For RECIST 1.1, a maximum of 5 target lesions can be recorded and measured at baseline with a maximum of 2 lesions per organ representative of all involved organs.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters which provides the reference point for assessing response at subsequent assessments.

Lymph Nodes

Measurable pathological nodes may be identified as target lesions if the short axis is ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. (For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as measurable).
Lymph nodes with ≥10 to <15mm short axis can be recorded as non-target, but not target, lesions.

8.5.2.2 Non-target Lesions

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis), as well as truly non-measurable lesions should be identified as non-target lesions and should also be recorded at baseline. Examples of lesions considered truly non-measurable are: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (8.5.3.7). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

8.5.2.3 Baseline Documentation of Lesions - irRC

Baseline scans will be assessed prior to availability of post baseline scans. Where possible, the same radiographer should review the scan for both RECIST and irRC at the same time, and review all scans for the same patient.

For irRC, up to five lesions in a single organ may be recorded with a maximum of 10 visceral and five cutaneous index lesions. At the baseline tumour assessment, the two largest perpendicular diameters of each target lesion are recorded and the sum of the products of the two largest perpendicular diameters of all index (target) lesions is calculated (SPD). At each subsequent tumour assessment, the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm) are added together to provide the total tumour burden:

$$\text{Tumour Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

8.5.3 Evaluation of Response

8.5.3.1 Evaluation of Target Lesion Response by RECIST 1.1

For each scan patients will be assigned a response by RECIST 1.1 according to the following rules:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.5.3.2 Evaluation of Target Lesion Response by irRC

For each scan patients will be assigned a response by irRC according to the following rules:

Complete Response (irCR): Disappearance of all target lesions.

Partial Response (irPR): At least a 50% decrease in the SPD, taking as reference the baseline calculation.

Progressive Disease (irPD): At least a 25% increase in the SPD taking as reference the smallest SPD on study (this includes the baseline sum if that is the smallest on study).

Stable Disease (irSD): Neither sufficient shrinkage to qualify for PR (compared to baseline) nor sufficient increase to qualify for PD (compared to the smallest SPD while on study).

8.5.3.3 Target Lesions that Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5mm. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned.

8.5.3.4 Target lesion lymph nodes.

For RECIST 1.1, lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study.

The actual short axis measurement of the nodes is included in the sum of target lesions and used to assess response as PR, SD or PD. However, in situations where lymph nodes are included as target lesions and complete response criteria are met, the 'sum' of lesions may not be zero since a normal lymph node is defined as having a short axis of <10mm.

8.5.3.5 Target Lesions that Split or Coalesce on Treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.

As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced

such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

8.5.3.6 Evaluation of Non-target Lesions (RECIST 1.1)

Even if some non-target lesions are actually measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

8.5.3.7 Unequivocal Progression in Non-target Disease

To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit considering discontinuation of therapy.

A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

8.5.3.8 New Lesions

The appearance of new malignant lesions denotes disease progression by RECIST 1.1, but not according to irRC.

The finding of a new lesion should be unequivocal: i.e., it is not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions; necrosis of a liver lesion may be reported on a CT scan as a 'new' cystic lesion, which it is not). This is particularly important when the patient's baseline lesions show partial or complete response.

Any lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered a new lesion.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, the date of the initial post-baseline scan is used for the date of the new lesion. Retrospective identification of target/non-target lesions at baseline is not permitted.

8.5.3.9 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response (for example if the criteria for PD are reached by the lesions that have been assessed).

8.5.3.10 Confirmatory Scans (RECIST 1.1 and irRC)

Confirmation of response (CR and PR) is required for RECIST 1.1 with the confirmatory scan being carried out at least 4 weeks after the scan from which a response was seen. Patients will then return to regular scheduled imaging every 8 weeks relative to the Week 12 scan (Cohort A) or Week 6 scan (Cohort B) and 12 weekly for patients still on study after Week 52. Patients who obtain a confirmation scan do not need to undergo scheduled imaging assessment 4 weeks later (e.g., if a patient obtains a scan at Week 16 to confirm a Week 12 response, their next scheduled scan would not be performed until Week 28, with no scan at Week 20).

Once a response is confirmed, repeat scans are not required to confirm subsequent instances of the same response.

Confirmatory scans for responses by irRC may be carried out at the discretion of the Investigator to assist in managing treatment on study.

If imaging shows PD, it is at the discretion of the Investigator whether to keep a patient on study treatment or to stop study treatment until imaging is repeated approximately 4 weeks later in order to confirm PD, per irRC recommendations.

If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per irRC.

If a confirmatory assessment is non-evaluable but the subsequent scan maintains the same response/progression, the response/progression can be considered confirmed (eg PR-NE-PR).

8.5.4 Immunological Marker Assessments

An exploration of tumour biomarkers to build on preclinical results observed for IMM-101 + CPIs which suggest an additive effect is planned for this study. Biomarkers that could help to understand and, potentially predict, clinical response to the combination of nivolumab and IMM-101 will be investigated in peripheral blood and in tumour specimens taken from patients prior to, and during study treatment.

All samples collected may also be used for future exploratory analyses.

Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

8.5.4.1 Tumour Sample Collection

For all patients in cohort A of the study, collection of tumour tissue is a Protocol requirement during Screening to evaluate the biomarker, PD-L1, that may be predictive of treatment benefit. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein. A newly obtained tumour biopsy is highly desirable and preferred, but an archival tumour specimen collected during the 3 months prior to Screening is acceptable. Sufficient quantity must be available to provide a minimum of 10 slides. Patients with an inadequate archived sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo one further re-biopsy at the discretion of the Investigator. The same sample is used for immunological marker assessment.

In addition, tumour biopsies from patients in cohort A will be scheduled at Week 12 (to be taken in the following 2 weeks) and will be obtained if possible from the same lesion as at Screening (or otherwise from another suitable lesion will be considered), subject to the patient providing consent.

For patients in cohort B, a biopsy sample at Screening will be taken subject to the patient's consent and also providing that scheduling the procedure will not cause any delay to the patient's treatment for those who are on-going with anti-PD1 therapy. Patients in cohort B who have provided a biopsy sample at Screening will also be asked for consent for a further biopsy sample taken, ideally, from the same lesion as at Screening if they should show a response to study treatment. If it is not possible to use the same lesion as at Screening, another lesion may be considered that is amenable to biopsy.

8.5.4.2 Serum Biomarkers/Whole Blood Sample

Blood samples for analysis of exploratory biomarkers will be taken from all patients in both cohorts of the study at Screening. For patients in cohort A, subsequent samples are taken at Week 4, Week 8, Week 12, Week 20 and every 8 weeks thereafter while the patient is on study until Week 52. For patients in cohort B, post-baseline samples are taken at Week 6, Week 14, Week 22 and every 8 weeks thereafter until Week 46 while the patient is on study. For cohort B, blood samples will be taken according to the same schedule following any change of study treatment to IMM-101 + ipilimumab.

8.5.5 ECOG/WHO Performance Status Assessment

To be eligible for entry into this study, patients must have an ECOG/WHO Performance Status of ≤1 at Week 0, Visit 1. The ECOG/WHO Performance Status assessment is provided in Appendix 2. Two observers will be required to assess performance status at the Screening and Week 0, Visit 1 assessments. If there is any discrepancy between the two scores, the highest (worst) assessment will be used. Subsequent assessments are at Week 4 and every 4 weeks thereafter on study and only require one assessor.

9. ASSESSMENT OF SAFETY AND TOLERABILITY

9.1 SAFETY AND TOLERABILITY PARAMETERS

One of the primary objectives of this study is to describe the safety profile of IMM-101 combined with nivolumab by assessing the incidence and frequency of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for nivolumab) for the combination of IMM-101 with nivolumab. For cohort A, the final analyses are at the end of the study or when all patients in this cohort have withdrawn if this is sooner but an additional interim safety data review will be performed after all patients in this cohort have had the opportunity for 1 year on study. For cohort B, the final analyses are at the end of study or when all patients in this cohort have withdrawn if this is sooner with an additional interim safety data review when all patients in this cohort have had the opportunity for 6 months on study.

An additional exploratory objective, for any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment, is the incidence and frequency of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for ipilimumab) following commencement of treatment with the combination of IMM-101 with ipilimumab assessed when all patients have had the opportunity for 6 months on study and again at the end of study.

In addition, reviews of all available safety data, to include AEs, biochemistry and haematology, and injection site reactions, will take place by the Sponsor and Investigator, every 6 months throughout the study, with a particular focus on immune-related AEs. Any signals identified that are believed to impact on patient safety may result in termination of the study.

The combined overall safety profile for IMM-101 including the data obtained from this study will be included in the DSUR annual submission in line with the IBD.

9.2 ADVERSE EVENTS

9.2.1 Adverse Event Definition

An AE is any untoward medical occurrence, in a subject or clinical investigation patient administered with a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

9.2.2 Adverse Drug Reaction

During early development studies when clinical experience with a new investigational product or its new usages is limited all noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Note that nivolumab and ipilimumab are considered non-investigational medicinal products for this study, used as background SOC for advanced melanoma. Only IMM-101 is considered as the investigational product for this study. Causality of adverse events to IMM-101 as well as to nivolumab and (where used) to ipilimumab will be recorded.

9.2.3 Relationship of Adverse Events

Assessment of causality of AEs to the study drug (IMM-101) and also to nivolumab and to ipilimumab (where used in cohort B) is according to the following guidelines:

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.

Note: Even if the Investigator feels there was no relationship to the study drug, the AE is to be reported.

9.2.4 Intensity of Adverse Events

All AEs (or toxicities) including local injection site reactions encountered during the study will be evaluated according to the NCI CTCAE v4.03

[23] grading system (0 to 5), where applicable.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

9.2.5 Treatment-Emergent Adverse Events

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

9.2.6 Unexpected Adverse Event/Adverse Drug Reaction

An unexpected AE/ADR is an AE/ADR for which the nature or severity is not consistent with the applicable product information (e.g., not clearly listed in the Reference Safety Information of the IB for an unapproved investigational product, or in the summary of product characteristics [SmPC] for an authorised product).

The term "expected" in pharmacovigilance is not used to describe an event which might be anticipated from knowledge of the pharmacological properties of a substance. An event is also not to be described as "expected", merely because it was foreseeable due to the health status (e.g., age, medical history) of the study patient. It refers strictly to the event being mentioned or listed in the applicable product information.

9.3 SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death (*other than due to disease progression, see Note below*).
- Is life-threatening*.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other medically important condition. For example conditions not included above but that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to the patient's underlying disease. Examples of important medical events which may also meet the definition of a SAE include: intensive treatment in an emergency room or at home for a reversible condition that did not result in hospitalisation (eg, allergic bronchospasm or convulsions).

* Life-threatening in the definition of a SAE or adverse reaction refers to an event in which the patient *was at risk of death at the time of event*; it does not refer to an event, which hypothetically might have caused death if it were more severe.

All of the above criteria apply to the case as a whole and should not be confused with the outcomes of individual reactions/events. More than one of the above criteria can be applicable to the one event.

All SAEs, whether or not deemed related to IMM-101, nivolumab or ipilimumab, including those considered expected or associated with protocol-specified procedures must be reported to the relevant pharmacovigilance contact within 24 hours of knowledge by email or fax in the format detailed by the SAE Reporting Form (see Section 9.7).
Note: Death of a cancer patient due to disease progression may be expected in a study of cancer patients. Therefore, SAEs/death due to disease progression will not be captured as an SAE if the SAE/death is, in the Investigator's opinion, expected as normal course of the disease. However, if the disease progression was faster than expected then an SAE will be reported.

9.3.1 Suspected Unexpected Serious Adverse Reaction

A suspected, unexpected serious adverse reaction (SUSAR) is defined as a suspected adverse reaction related to the study drug which occurs during the study, and that is both unexpected (i.e., not previously identified in nature, severity, or degree of incidence based upon the current IB, Section 8) and serious.

For all SAEs the Investigator and Sponsor (or designee) will independently assess whether there is a reasonable possibility that the event may have been caused by IMM-101 ("drug-related"). If the SAE is assessed to be drug-related by the Investigator or the Sponsor and is also unexpected, the Sponsor (or designee) will report it to the appropriate Regulatory Authorities and Ethics Committees and notify Investigators as required by applicable local regulations.

SUSARs are required to be reported within 7 calendar days for life threatening events and those resulting in death, or 15 calendar days for all others. These timeframes begin with the first notification of the SUSAR to the Sponsor/designee.

As nivolumab and ipilimumab are non-investigational products, any SAEs that are considered by the Investigator to be related to these products will be reported if it is considered a possibility that the SAE is a result of an interaction between IMM-101 and nivolumab or between IMM-101 and ipilimumab or if the adverse reaction is considered by the Sponsor as likely to affect the safety of patients in the study. Other adverse reactions considered related to nivolumab or ipilimumab, but not to IMM-101, will be reported by the Sponsor (or designee) to the applicable regulatory authority as post-approval SAEs.

9.4 LABORATORY EVALUATION

Clinical laboratory evaluations will be assessed (prior to administration of IMM-101) using the parameters and timelines presented in **Table 1**.

Abnormal laboratory test results considered to be clinically significant will be recorded as an AE in the patient's eCRF and the patient will be followed-up until the laboratory value has returned to normal range or stabilised at a non-clinically significant value.

Any additional blood tests to those scheduled in this study will be performed as per the Investigator's routine procedures.

9.5 ASSESSING AND RECORDING SAFETY PARAMETERS

All AEs will be recorded on the patient's eCRF from the time of informed consent. All AEs will be followed until resolution, death, or 30 days after the last administration of study treatment (whichever comes first). The Investigator may contact the patient by telephone to obtain the information. Related SAEs will be recorded regardless of time from last dose and added to the eCRF if the occurrence is prior to final Investigator sign-off of the eCRF. SAEs will be recorded up to 30 days from the last administration of study treatment. All SAEs will be followed up until resolution or stabilisation.

Injection site reactions will be assessed by type and grade and recorded in the patient's eCRF before each injection of IMM-101. These will only be recorded as an AE if deemed appropriate by the Investigator, but any injection site reactions of Grade ≥3 (Section 9.2.4) should be recorded as an AE.

9.6 APPROPRIATENESS OF MEASUREMENTS

All laboratory and other safety assessments (vital signs, weight, physical examination, pregnancy tests, etc.) are regarded as standard, i.e., are widely used and generally recognised as reliable, accurate and relevant.

For all patients in the study, the maximum volume of blood collected per patient at a single visit specifically for the safety endpoints will not exceed 10mL. For patients in cohort A, an additional 25mL of whole blood will be taken for immunological marker analysis at Screening,

Week 4, Week 8, Week 12, Week 20, and every 8 weeks thereafter until Week 52 or EOS, if this is sooner. For patients in cohort B, an additional 25mL of whole blood will be taken for immunological marker analysis at Screening, Week 6, Week 14, Week 22, and every 8 weeks thereafter until Week 46 or EOS, if this is sooner.

Due to the need to evaluate the biomarker, PD-L1, that may be predictive of treatment benefit, biopsy samples are collected at Screening from all patients in cohort A of the study. Subsequent tumour biopsies from patients in cohort A at Week 12 will be valuable in exploratory research into biomarkers that may help to further elucidate the activity of the IMM-101 + nivolumab combination. However, the collection of samples is subject to the patient providing consent. For patients in cohort B, a biopsy sample at Screening will be taken subject to the patient's consent and also providing that scheduling the procedure will not cause any delay to the patient's treatment for those who are on-going with anti-PD1 therapy. Patients in cohort B who have provided a biopsy sample at screening will also be asked for consent for a further biopsy sample taken from the same lesion as at Screening if they should show a response to study treatment.

9.7 RECORDING AND REPORTING ADVERSE EVENTS AND INTERCURRENT ILLNESSES

It is the responsibility of the Investigator to document all AEs that occur during the study from patient entry (i.e., informed consent). An AE includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes whether or not associated with the study drug and whether or not considered related to the study drug. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or drug interaction. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Patient entry into the study is defined as the time at which informed consent is obtained (this must be before any protocol-specific diagnostic procedures or interventions). All AEs that occur after informed consent has been provided must be reported regardless of whether or not they are considered drug related.

Adverse events will be elicited by asking the patient a non-leading question, for example “Have you experienced or are you experiencing any new or changed symptoms since we last asked/since your last visit?” All AEs must be reported on the appropriate page of the patient's eCRF.

All AEs occurring in patients receiving nivolumab or ipilimumab should be reported irrespective of whether they are identified as being expected as per the product labelling or not.

Each AE will be assigned a CTCAE severity/intensity category as described in Section 9.2.4.

If there is a change in severity of an AE, it must be recorded in the patient's eCRF.

Every effort should be made by the Investigator to explain each AE and assess its relationship, if any, to study drug treatment (IMM-101, nivolumab and, if used on study for patients in cohort B, ipilimumab). Causality should be assessed using the categories as described in Section 9.2.3.

The Investigator must report in detail all adverse signs and symptoms following obtaining informed consent which are either volunteered by patients or observed during or following the course of investigational product administration.

In the event of a SAE/SUSAR, the Investigator will also complete the SAE Report form and forward to Bionical-Emas, by email or fax, within 24 hours:

SAE CONTACT DETAILS: Bionical-Emas Ltd.
63-65 Knowl Piece, Wilbury Way, Hitchin, Hertfordshire, SG4 0TY, UK.
Tel.: +44 (0)1462 422717
Fax: +44 (0)1462 600456
Email: **Drug.Safety@bionical-emas.com**

The IEC must be informed if the serious or unexpected adverse reaction, in the opinion of the Sponsor or the Investigator, is likely to affect the safety of the patients or the conduct of the study.

Expedited reporting is not usually required:

- For reactions which are serious but expected
- For non-serious adverse reactions whether expected or not
- For events considered unrelated to the investigational medicinal product.

9.7.1 Pregnancy Reporting

Pregnancy is not considered an SAE. If a female participant, or the female partner of a male participant, becomes pregnant after exposure to study product, the pregnancy must be reported to Bionical-Emas within 24 hours of the Site Staff becoming aware of the Pregnancy. A Pregnancy Reporting Form must be completed and emailed or faxed to Bionical-Emas.

In the event of a pregnancy being reported after exposure to study product, the pregnant woman should be followed to completion/termination of the pregnancy and the outcome of the mother and infant should be reported in follow-up using the Pregnancy Reporting Form.

If a congenital anomaly or birth defect occurs, this must be reported to Bionical-Emas by the submission of a completed SAE form.

9.8 ADVERSE EVENT FOLLOW-UP PROCEDURES

All SAEs will be followed to resolution. All non-serious AEs will be followed until the event has resolved (disappeared) or until they have stabilised, and the relationship to the study drug is clarified. AEs will be followed until resolution, death or 30 days after the last administration of study treatment (whichever comes first). The Investigator may contact the patient by telephone to obtain the information.

10. EFFICACY ASSESSMENTS

10.1 OVERALL RESPONSE RATE

In this study, Overall Response Rate (ORR) is calculated from assessments of Best Overall Response (BOR) per RECIST 1.1. ORR is defined as the number of patients with a BOR of CR or PR divided by the number of ITT patients in each cohort of the study. For cohort B, ORR will be evaluated from assessments of BOR up until the point of change of treatment on study to IMM-101 + ipilimumab, where applicable. An interim data review on each respective cohort will be conducted after all cohort B patients have had the opportunity for 6 months on study, and when all cohort A patients have had the opportunity for 12 months on study.

ORR calculated from BOR according to Immune-Related Response (irRC) will be used as a secondary efficacy parameter and will be calculated similarly.

10.1.1 Overall Response

10.1.1.1 Overall Response by RECIST 1.1

For RECIST 1.1, Overall Response at any time point is evaluated based on target lesion response, non-target lesion response and any new lesions identified on a post-baseline scan. An Overall Response of CR, PR, SD, or PD at each scan assessment is made according to the guidelines in **Table 2**:

Table 2: Time Point Overall Response - RECIST 1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Not all evaluated	Non-PD	No	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

10.1.1.2 Overall Response by irRC

For irRC, overall response at any time point is evaluated on the change in tumour burden which is calculated from index (target) and new, measurable lesions only:

Tumour Burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Non-measurable lesions do not contribute to the tumour burden. However, new non-measurable lesions (ie < 5 x 5 mm) do preclude assigning CR.

Overall Response is evaluated according to the following rules:

Complete Response (irCR): Disappearance of all target lesions; no new lesions that are either measurable or non-measurable.

Partial Response (irPR): At least a 50% decrease in tumour burden, calculated as above, taking as reference the baseline SPD calculation.

Progressive Disease (irPD): At least a 25% increase in tumour burden taking as reference the lowest tumour burden on study (this includes the baseline SPD if that is the smallest on study).

Stable Disease (irSD): Neither sufficient shrinkage in tumour burden to qualify for PR (compared to baseline) nor sufficient increase to qualify for PD (compared to the smallest tumour burden while on study).

10.1.2 Best Overall Response

Best Overall Response (CR, PR, SD or PD) is determined as the best response designation, recorded from the first post-screening scan until and including the last imaging assessment on study for each patient. All scans will be evaluated for overall response and BOR will be calculated based on overall response designations determined by the Investigator, from all scan assessments. However, for any patients in cohort B who change treatment on study to IMM-101 + ipilimumab, BOR will be assessed both before a change to ipilimumab for patients to whom this applies (for evaluation of ORR), and also from all tumour assessments on study.

BOR according to both RECIST 1.1 criteria and irRC criteria will be determined.

For cohort A, BOR will be assessed at the time point when all patients have had the opportunity for 12 months on study (RECIST 1.1 only), and again at the end of the study. For the first assessment, the BOR will be the best response designation, as determined by the Investigator, recorded from the first post-screening scan until the last scan prior to or at the 12 month time point for each patient on study.

For cohort B, BOR will be assessed at the time point when all patients have had the opportunity for 6 months on study (RECIST 1.1 only) and again at the end of study or when all patients in this cohort have withdrawn if this is sooner. For the first assessment, the BOR will be the best response designation, as determined by the Investigator, recorded from the first post-screening scan until the last scan prior to or at the 6 month time point for each patient on study. For any patients in cohort B of the study who change treatment on study to IMM-101 + ipilimumab, BOR will be assessed both before a change to ipilimumab for patients to whom this applies (for evaluation of ORR), and also from all tumour assessments on study.

In this study, the minimum scan time from Screening for determination of SD will be 9 weeks.

Confirmed response is used for calculation of BOR (Section 8.5.3.10); however unconfirmed results will also be analysed and corresponding BOR and ORR reported for comparability with published data.

10.1.3 Duration of overall response

The duration of overall response is defined as the time from the date of first post-baseline scan with documented response per RECIST 1.1 (calculated for patients with a response of CR or PR (including patients with unconfirmed responses)) until the time when progressive disease is objectively documented per RECIST 1.1. or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumour assessment. Duration of response is evaluated for responders (CR or PR) only. For any patients in cohort B who change treatment on study to IMM-101 + ipilimumab, only responses evaluated until the point of this change in therapy are included.

10.1.4 Time to Response

Time to Response is defined as the time from first post-Screening visit (Week 0, Visit 1) to first post-baseline scan with documented PR or CR by RECIST 1.1 (including any patients with unconfirmed responses). Time to response is evaluated for responders (CR or PR) only. For any patients in cohort B who change treatment on study to IMM-101 + ipilimumab, only responses evaluated until the point of this change in therapy are included.

10.2 PROGRESSION FREE SURVIVAL (PFS)

PFS is defined as the time between the date of the first post-Screening visit (Week 0, Visit 1) and the first date of documented progression, according to RECIST 1.1, as determined by the Investigator from CT/MRI scans, or death due to any cause, whichever occurs first.

Patients who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumour assessment. Subjects who did not have any on study tumour assessments (scans) and did not die will be censored on the date of first post-Screening visit. Subjects in cohort B who change therapy on study to IMM-101 + ipilimumab without documented progression by RECIST 1.1 will be censored at the date of their last evaluable tumour assessment (scan) prior to this change in therapy.

10.3 OVERALL SURVIVAL

OS is defined as the time from enrolment to death due to any cause. OS will be expressed from time of enrolment in this study. Patients completing or withdrawing from the study will be followed up for post-study survival information until database lock and at this point, any patients without a death date will be censored at the date the patient was last known to be alive. The 1-year OS rate will be calculated.

10.4 PD-L1 STATUS

The endpoint of BOR will be assessed for subgroups based on PD-L1 status (positive and negative/indeterminate) for subjects in cohort A of the study only. The following definitions apply:

PD-L1 positive: ≥ 5% tumour cell membrane staining in a minimum of a hundred evaluable tumour cells.

PD-L1 negative: < 5% tumour cell membrane staining in a minimum of a hundred evaluable tumour cells).

PD-L1 indeterminate: tumour cell membrane scoring hampered by high cytoplasmic staining or melanin content.

10.5 ECOG/WHO PERFORMANCE STATUS ASSESSMENT

The ECOG/WHO Performance status will be recorded at Screening, at Visit 1 and every 4 weeks thereafter while the patient is on study.

10.6 DISEASE CONTROL

Disease Control will be assessed for patients in cohort B of the study only and is defined as those patients with a response (CR or PR) or SD based on RECIST 1.1. The minimum scan time from Day 0 (date of first IMM-101 dose) for determination of Stable Disease (SD) is 9 weeks. Stable disease for patients in Cohort B can therefore be first assessed at the second scan on study (Week 14) since the first scheduled scan is at 6 weeks. If unscheduled scans take place earlier than Week 14 but later than Week 9, these may be used for determination of SD. The disease control rate is evaluated for treatment with IMM-101 + nivolumab only and is the number of patients with disease control at each scheduled scan time point divided by the number of patients in cohort B. For patients who change treatment to IMM-101 + ipilimumab, disease control is assessed until and including the last evaluable tumour assessment (scan) prior to the change in therapy, and the disease control rate evaluated accordingly.

10.7 IMMUNOLOGICAL MARKER ASSESSMENTS

Biomarkers that could help to understand and, potentially predict clinical response to the combination of IMM-101 and nivolumab will be investigated in peripheral blood and in tumour specimens taken from patients in cohort A of the study during Screening and on study as detailed in Sections 8.5.4.1 and 8.5.4.2. Blood samples from patients in cohort B of the study will also be used as part of this investigation and tumour specimens if available (Section 8.5.4.2).

All samples collected may also be used for future exploratory analyses to assess biomarkers associated with study treatment. The results of all these analyses will be reported separately to the main study results.

Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

11. STATISTICS

11.1 STATISTICAL METHODS

The statistical methods used will be appropriate to the objectives of the study and the nature of the data. A brief description of the planned statistical methods and data presentations is described in this protocol. A detailed Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more detailed and technical description (including templates for Tables, Listings, and Figures) of the planned presentation of the results. The final SAP will include both the final analysis plan and the plan for interim data reviews and will be approved before conducting the first interim data review (either following the 12-month assessment for all patients in cohort A or following the 6-month assessment for all patients in cohort B, whichever occurs first).

Evaluation of safety and efficacy will be assessed by cohort. The primary time point of the study is after all patients have had the opportunity for 18 months of study treatment. The by-cohort interim data reviews (conducted when all cohort A patients have had the opportunity for 1 year on study (cohort A) and for 6 months on study (cohort B) and/or final analysis may be conducted for each cohort separately or together, depending on recruitment rates.

All endpoints will be presented descriptively only, with no formal statistical analysis planned.

11.1.1 Methods of Analysis

Descriptive evaluation of the efficacy and safety endpoints will be performed using summary statistics (number of patients [n], mean, standard deviation [StD], median, minimum, maximum) for continuous data endpoints and frequency counts and percentages for categorical data endpoints. Percentages will be calculated using the total patients in the respective analysis set.

All AEs and procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) drug dictionary and all concomitant treatments will be coded using the World Health Organisation (WHO) Drug Dictionary. All patient data will be presented as data listings by cohort.

Exact 95% binomial confidence intervals (CIs) will be calculated for the observed ORR (using RECIST 1.1 and irRC criteria) and disease control rate (cohort B only). Overall survival, PFS, duration of and time to response (RECIST 1.1) will be summarised by Kaplan-Meier (KM) methods and presented graphically where appropriate. The median OS (if applicable) and 1-year OS rate will be estimated for both cohorts.

11.1.2 Baseline Demographics

The study population of each cohort will be described descriptively in terms of baseline demographics, disease history and baseline disease status (including stage (both 8th edition of the AJCC melanoma staging system and M staging), PS, BRAF and PD-L1 status, prior melanoma cancer therapies), relevant medical history, prior and concomitant medication/procedures and exposure, compliance and treatment modifications with IMM-101 and nivolumab and those receiving treatment with IMM-101 + ipilimumab where relevant for patients in cohort B.

11.1.3 Safety and Tolerability Endpoints

The primary safety endpoints include the following:

- Incidence, frequency and severity of AEs, Serious AEs, treatment-related AEs (related to IMM-101 and/or nivolumab/ipilimumab (as applicable), immune-related AEs (as listed in the SmPC for nivolumab), Grade 3 and above AEs and AEs leading to IMM-101 discontinuation or study withdrawal throughout the study.

The secondary safety endpoints include the following:

- Incidence and frequency of laboratory parameter abnormalities
- Change from baseline values in laboratory parameter values
- Incidence and frequency of local injection site reactions.

Exploratory safety endpoints include the following:

- For the subgroup of patients in cohort B who receive IMM-101 + ipilimumab as subsequent treatment: The incidence, frequency and severity of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for ipilimumab) experienced following the start of ipilimumab treatment up to the end of the study.

Treatment-emergent AEs (TEAEs) are defined as AEs occurring after the first dose of IMM-101. Only TEAEs will be presented in summary tables and all AEs (i.e., TEAEs and non-TEAEs) will be listed by patient within cohort.

TEAEs will be summarised by MedDRA system organ class and preferred term using standard incidence and frequency tables. The incidence of TEAEs will be presented as the proportion of patients with at least one AE by system organ class and preferred term and frequency of TEAEs will be calculated as the number of events by system organ class and preferred term.

Treatment-related AEs are defined as AEs which are related to study treatment (IMM-101 and/or nivolumab, and/or ipilimumab if after ipilimumab dosing in cohort B). Related AEs will be those assigned by the investigator as definitely, probably or possibly related to study treatment or with an unknown relationship. Relatedness will be assessed to each of IMM-101, nivolumab and ipilimumab separately as well as for the combined treatment combination. The incidence and frequency of treatment-related AEs, SAEs, and immune-related AEs will be presented, as for all TEAEs.

For cohort B patients, only TEAEs occurring prior to the start of treatment with IMM-101 + ipilimumab or TEAEs assessed as related (i.e. definitely, probably or possibly related) to nivolumab will be included in the primary safety endpoint evaluations. For the exploratory evaluation of safety, only TEAEs occurring after the start of treatment with IMM-101 + ipilimumab will be included (including any TEAEs related to nivolumab but occurring after the start of ipilimumab).

Grade 3 and above AEs, AEs leading to study withdrawal and AEs leading to death will be summarised by cohort, if present, and listed as above.

The incidence, frequency and severity and type of all TEAEs (following the start of IMM-101 administration, regardless of combination therapy received) will be included in the data presentations, for the combined cohorts.

11.1.4 Other Safety Endpoints

Safety Laboratory Parameters

Laboratory parameter results will be summarised descriptively for continuous parameters, by assessment time point using summary statistics of actual values and change from baseline values. In addition, ‘shift’ tables of the number and percentage of patients with values outside normal range and within normal range at post baseline assessments by baseline assessment will be presented. Abnormal values will be flagged in data listings.

Vital Signs, weight and 12-lead ECG.

Vital signs, and weight data will be summarised by presenting summary statistics of actual values and change from baseline values. Vital signs monitoring on the day of first administration of IMM-101 will be listed only. The Investigator’s overall evaluation of

12-Lead ECG findings including clinical significance determination will be listed by assessment time point.

Injection Site Reactions

The frequency of injection site reactions by type of reaction will be summarised. In addition, the patient's worst recorded reaction grade by reaction type across all assessments will be summarised.

Other Safety Parameters

All other safety data will be summarised using descriptive statistics or frequency counts as applicable and listed.

11.1.5 Efficacy Endpoints

The Primary efficacy endpoint is the ORR defined as the number of patients with a BOR of CR or PR assessed, for each patient between the first post-baseline scan until and including the last imaging assessment on study (including all scheduled and unscheduled scans) for each patient, divided by the number of patients in the ITT set, in each cohort of the study. BOR is defined in Section 10.1.2.

The observed ORR will be presented using a frequency table including the number and percentage of patients with a BOR of CR or PR and exact 95% binomial CIs will be presented.

Confirmed response is used for calculation of BOR (Section 8.5.3.10); however unconfirmed results will also be analysed in a sensitivity analysis of the primary efficacy endpoint and corresponding BOR and ORR reported for comparability with published data. Further sensitivity analyses will be conducted using BOR until disease progression (RECIST 1.1 criteria), in the event that there are patients with PR or CR responses following disease progression.

Secondary efficacy endpoints:

- Progression-free survival (PFS) assessed by RECIST 1.1 at the end of the study.

Progression-free survival is defined in Section 10.2 and will be summarised by Kaplan-Meier (KM) methods and presented graphically.

- Overall survival (OS) and OS at 1 year

Overall survival is defined in Section 10.3 and will be summarised by KM methods and presented graphically. The median OS (if applicable) and survival rate at 1 year will be estimated and summarised.

Exploratory efficacy endpoints:

- ORR assessed by irRC criteria for both cohorts at the end of the study

The ORR will be calculated as for the primary endpoint, based on a BOR of CR or PR (by irRC criteria), see definition in Section 10.1.2 and presented as for the primary endpoint.

- Duration of overall response and time to response by RECIST 1.1, for both cohorts at the end of the study

The duration of overall response is defined in Section 10.1.3 and time to response is defined in Section 10.1.4. These endpoints will be evaluated for responders only and will be summarised using KM methods and presented graphically where appropriate.

- Disease control rate (for patients in cohort B)

Disease control is defined in Section 10.6. The disease control rate will be assessed by assessment time point for patients in cohort B of the study only and is defined as the percentage of those patients with a response (CR or PR) or SD based on RECIST 1.1 and assessed at each scan assessment time point from Week 14 onwards to the end of the study (or to last scan prior to commencement of treatment with IMM-101 + ipilimumab if applicable).

- Best Overall Response for patients in cohort B, to include any responses during treatment with IMM-101 + ipilimumab

  The BOR rate for cohort B will be assessed including any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab. All tumour assessments on study (scheduled and unscheduled scan assessments) are included in this evaluation. The BOR will be listed by cohort B patient in this subgroup and the rate will be summarised using frequency counts and percentages.

11.1.6 Interim Data Review

By cohort interim data reviews will be conducted for ORR (RECIST 1.1) and incidence, frequency and severity of AEs, when all cohort A patients have had the opportunity for 1 year on study (cohort A) and after 6 months on study (cohort B). No other parameters will be presented at the interim analysis time points. The by-cohort interim analyses may be conducted for each cohort separately or together, depending on recruitment rates.

The interim data reviews will be conducted on the Intent-to-Treat (ITT) analysis set only (see Section 11.7.1).

ORR will be defined as the number of patients with a BOR of CR or PR divided by the number of ITT patients in each cohort of the study. The BOR will be determined once all the data up to and including the last assessments are available at the applicable time point. It is defined as the best response designation, as determined by the investigator, based on confirmed responses according to RECIST 1.1, recorded between the date of first post-screening scan and the date of last scan at/prior to the assessment at the 12-month assessment (cohort A) and 6-month assessment/last assessment prior to change of treatment to IMM-101 + ipilimumab whichever the sooner (cohort B).

The interim safety data reviews will include all AEs reported in the study and in the database at the time of interim database lock for the 12-month (cohort A) and 6 month (cohort B) interim data reviews.

11.2 SAMPLE SIZE

Sufficient patients will be screened for 18 patients to be enrolled into cohort A and 8 into cohort B of this open-label study. Patients withdrawn after first treatment with IMM-101 will not be replaced. No formal sample size calculation has been performed and the sample size is considered a sufficient and adequate number of patients to investigate the efficacy signals of IMM-101 combined with nivolumab in controlling advanced melanoma and to explore the safety profile of the combination therapy.

11.3 LEVEL OF SIGNIFICANCE

In this non-comparative study, all endpoints will be presented descriptively only, with no formal statistical analysis performed. Hence no formal statistical hypothesis testing will be carried out. The interpretation of p-values will be in the descriptive sense only and no levels of significance will be applied.

11.4 CRITERIA FOR THE TERMINATION OF THE STUDY

No statistical stopping rules will be formulated for this study. Additional criteria for termination are described in Section 18.7.

11.5 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED AND SPURIOUS DATA

Missing, unused and spurious data will be treated and listed as such in data listings. Rules for handling missing data for specific endpoints and data derivations in the data presentations will be fully detailed in the SAP.

11.6 DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

Any deviations from the original statistical plan as described in this Protocol will be agreed by the Sponsor and documented and justified in a Protocol Amendment, the final SAP or the clinical study report, as appropriate.

11.7 PATIENT SELECTION FOR ANALYSES

11.7.1 Analysis Sets

The efficacy and tolerability endpoints will be evaluated using the Intent-to-treat (ITT) set, defined as all patients receiving at least one dose of IMM-101, irrespective of compliance with eligibility and other protocol criteria. This set will also define the Safety set.

In addition, a Per-protocol (PP) set, defined as ITT patients with no major protocol deviations and having complied with the treatment regimens of the combination therapy, will be used to evaluate further the efficacy of the combination therapy for the primary and secondary efficacy parameters.

The data for any enrolled patients who are not in the ITT set (i.e., who do not receive at least one dose of IMM-101) will be listed only.

11.7.2 Subgroups For Analysis

Subgroups of patients in both cohorts will be defined based on BRAF status (Wild type, Mutant), Disease stage (M staging:- M1c (if Cohort B, combined with M1d), M0 combined with M1a and M1b) and LDH at baseline (≤ ULN, > ULN categorisation). Subgroups of patients in cohort A will be defined based on PD-L1 status (PD-L1 positive and PD-L1 negative/indeterminate) at Screening. These subgroups will be summarised for the primary endpoint of ORR (RECIST 1.1) at the end of the study.

A subgroup of patients in cohort B will be defined as those cohort B patients who receive IMM-101 + ipilimumab as subsequent treatment (Cohort B IMM-101 + ipilimumab subgroup). This subgroup will be assessed for the primary safety endpoints of the incidence and frequency of adverse events, serious adverse events, treatment-related adverse events and immune-related adverse events (as listed in the SmPC for ipilimumab) experienced following the start of ipilimumab treatment up to the end of the study.

All subgroups will be summarised provided the respective subgroup size is at least 33% of the total size of the ITT set for cohort A and in cohort B, if at least 50% of the cohort B subjects are in the respective subgroup.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1 SOURCE DATA

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

12.2 SOURCE DOCUMENTS

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries and questionnaires or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

12.3 DIRECT ACCESS

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to the evaluation of a clinical study. Any party (e.g., domestic and foreign regulatory authorities, Sponsor or Contract Research Organisation (CRO) monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

The clinical monitor(s) should be given direct access to primary patient data (i.e., source data) which supports the data on the eCRFs for the study, i.e., hospital notes, appointment books, original laboratory records, etc. Because this enters into the realm of patient confidentiality, this fact must be included in the ICF that the patient signs. Other authorised persons such as auditors may need to have direct access to this source data

13. QUALITY CONTROL AND QUALITY ASSURANCE

An independent audit at the study site may take place at any time during or after the study. The independent audit may be carried out by the Quality Assurance (QA) department of a CRO, or the QA department of the Sponsor. In addition, an inspection may be carried out by a regulatory authority.

13.1 QUALITY CONTROL

Quality Control is defined as the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

13.2 QUALITY ASSURANCE

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

13.2.1 Inspection

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's and/or CRO's facilities, or at any other establishments deemed appropriate by the regulatory authorities.

13.2.2 Audit

An Audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the Protocol, designated SOPs, GCP and the applicable regulatory requirements.

14. ETHICS

14.1 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance to this Protocol, and in accordance with the provisions of the current guidelines of the WMA Declaration of Helsinki, as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013, the guidelines of ICH-GCP (CPMP/ICH/135/95), designated SOPs, and with local laws and regulations relevant to the use of new therapeutic agents.

In addition, this study will be undertaken in accordance with the Protocol and GCP on the conducting and monitoring of clinical studies. The IEC must be constituted according to the local laws/guidelines.

14.2 INDEPENDENT ETHICS COMMITTEE

Before initiating a study, the Investigator must have written and dated approval/favourable opinion from the relevant IEC for the study Protocol (and any amendments), written ICF,

consent form, patient recruitment procedures (e.g., advertisements), and any other written information to be provided to patients. Approval will be indicated in writing with reference to the final Protocol number and date. Details of the IECs constitution including names of its members and what function they perform on the committee (e.g., chairman, specialist, lay member) should be made available to the Sponsor and/or CRO.

During the study the Investigator must provide to the IEC all documents that are subject to review.

The Sponsor will supply the IB, Protocol and Patient Information Sheet and Consent Form to the Investigator for submission to the IEC for review and approval. Verification of the IECs unconditional approval of the Protocol will be transmitted to the Sponsor before the start of the study. This approval must refer to the study by exact Protocol title and number, identify the documents reviewed and state the date of review.

14.3 INFORMED CONSENT

The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study before Protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC. Patients, their relatives, or if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The Investigator will explain the nature, purpose and risks of the study and provide the patient with a copy of the Patient Information Sheet. The patient will be given sufficient time to consider the study's implications before deciding whether or not to participate.

Consent forms must be in a language fully comprehensible to the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IEC/IRB and signed by the patient and the Investigator obtaining the consent. The ICF will also be annotated with the study patient number.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the patient's dated signature. The signature confirms the consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and the Sponsor.

Should there be any amendments to the Final Protocol, such that would directly affect the patient's participation in the study, e.g., a change in any procedure, the ICF must be amended to incorporate this modification and the patient must agree to sign this amended ICF indicating that they re-consent to participate in the study.

Patients will be instructed that they are free to obtain further information from the Investigator at any time and that they are free to withdraw their consent and discontinue participation in the project at any time without prejudice.

The prospective patient will also be advised that access to medical records would be required and his/her GP will be informed of the patient's intention to participate in this study.

The written consent document will include permission for the Investigator or designee to contact the patient's GP for continued collection of survival data in the event of withdrawal.

14.4 MODIFICATION OF PROTOCOL

The Investigator should not implement any deviation from, or changes of, the Protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the competent authority and IEC of an amendment (defined as substantial). The only exceptions are where it is necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistic or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]).

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed Protocol amendment(s) should be submitted:

a) To the IEC for review and approval/favourable opinion,

b) To all relevant regulatory agencies.

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the Sponsor and the Chief Investigator. The Sponsor (or its designated CRO) will ensure that the Investigator submits necessary Protocol amendments to the appropriate IEC.

All agreed Protocol amendments must be clearly documented using standard procedures as defined by the Sponsor and must be signed and dated by the Sponsor and all Investigators.

14.5 ANNUAL REPORT

Immodulon (or designee) will be responsible for preparing the Annual Report of the study status and submitting to the Regulatory Authorities and Ethics Committee in the UK.

14.6 END OF STUDY NOTIFICATION AND SUBMISSION OF SUMMARY REPORT

Immodulon (or designee) will be responsible for preparing and submitting the End of Study Notification to the Ethics Committees and Regulatory Authorities in the EU Member States in which the study has been conducted. This must be submitted within 90 days of the end of the study (15 days if the study is terminated early).

For this purpose, the end of the study (study completion) is defined as the date of the last visit of the last patient undergoing this study. In the event that the last patient in the study dies before their last visit, the study completion will be the date that Immodulon was notified of the death. Any change to this definition is considered a significant amendment and MUST be notified to (and prior approval sought from) the Ethics Committees and the Regulatory Authorities concerned.

Immodulon (or designee) will be responsible for preparing and submitting a summary of the study results to the Ethics Committee (and Regulatory Authorities if required) in each Member State in which the study was conducted within 12 months of the end of the study.

Immodulon will be responsible for uploading the End of Study summary results to the European Clinical Trials Register European Union Drug Regulating Authorities Clinical Trials (EudraCT) as per the Commission guideline on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006.

15. DATA HANDLING AND RECORD KEEPING

15.1 DATA MANAGEMENT

An eCRF and study database will be created to capture and store study data. All study data will be processed and stored in a secure database located in the UK.

The Investigator, or delegate, will be responsible for entering data directly into the study database via a secure internet connection, according to instructions provided for data entry. During data entry, range checks, plausibility checks, and consistency checks will be performed to ensure accuracy and completeness of the data being collected. Data queries will also be generated and resolved according to the pre-prepared data management plan. At pre-determined time points, Statistical Analysis System (SAS®) datasets will be generated from the study database ready for analysis. A complete audit trail of all corrections will be available for inspection.

When data have been entered reviewed and edited, the Investigator will be notified to review and sign the eCRF electronically as per the agreed project process, data will be locked to prevent further editing, and a copy of the eCRF will be archived at the Investigator's site.

15.2 COMPLETION OF ELECTRONIC CASE REPORT FORMS

Data will be collected and recorded in an eCRF using an EDC system. Data entered in the eCRF are stored in a centralised database on a remote server. Data will be entered by the site personnel who can access the system through a personal user identification (ID), password and memorable data assigned by the System Administrator. The user ID, password and memorable data will be sent directly to the respective person in separate e-mails. Data will be entered directly into the eCRF via a single data entry process. The data entry activities are regulated and described in the Data Management Plan.

Data reported on the eCRF that are derived from source documents must be consistent with the source documents or the discrepancies should be explained.

15.3 ARCHIVING

According to ICH-GCP, the documents which should be archived are 'essential documents' which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.

Source documentation must also be archived. This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or CRFs and research related records held in support departments. All hard copies of source documents must be retained. If electronic records of documents exist these must be backed up and retained with the hard copies.

Essential documents should be retained until at least 2 years after the last approval of all outstanding marketing application(s) in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Essential documents may need to be retained for a longer period than determined in ICH-GCP depending on local regulations. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.

16. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with the Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and the Sponsor, in advance of the study commencing.

The Sponsor has insurance coverage for study related medicine-induced injury and other liabilities incurred during clinical studies which will provide compensation for any study related injury according to local laws and regulations. Immodulon will follow the ABPI guidelines which recommend that the sponsor company, without legal commitment, should compensate subjects without the need for proof of fault. Immodulon Limited will not compensate for when an injury was sustained outside of the protocol, or the protocol was not followed, or as a result of the Investigators' instructions not being followed.

17. PUBLICATION POLICY

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to regulatory authorities. The following conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning the investigational product (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by the Sponsor and not previously published) is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator agrees not to use it for other purposes without the Sponsor's written consent.

It is understood by the Investigator that the Sponsor will use the information obtained during this clinical study in connection with the development of the investigational product and therefore it may be disclosed, as required, to other Sponsor Investigators or any appropriate International Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results. Before submitting the results of this study for publication or presentation, the Investigator will allow the Sponsor 30 days in which to review and comment upon the publication manuscript. The Sponsor agrees that before it publishes any results of this study, it shall provide the Investigators at least 30 days for full review of the publication manuscript. In accordance with generally recognised principles of scientific collaboration, co-authorship with any Sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

18. ADMINISTRATIVE PROCEDURES

18.1 STUDY PERSONNEL

Before the start of the study, each Investigator must supply the Sponsor with the names and *curricula vitae* of the clinically responsible Co-Investigators of the study and the names of other possible participants and their professional backgrounds (e.g., medical doctor, nurse, etc.).

18.2 STUDY MONITORING

The Sponsor is responsible for ensuring the proper conduct of the study with regards to Protocol adherence and validity of the data recorded on the eCRF. The clinical monitor's duties are to aid the Investigator in the maintenance of complete, legible, organised and easily retrievable

data. In addition, a clinical monitor will explain, interpret and ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of a pharmaceutical product and ensure an understanding of the Protocol, reporting responsibilities and the validity of the data.

The clinical monitor will perform a combination of remote and/or on-site monitoring. Remote monitoring may be used to review the CRFs for completeness and adherence to the Protocol. On-site monitoring will be performed to check the CRF data against the source documents, including the informed consent.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data entered on the eCRFs and in all required reports. Data entered on the eCRF, which are derived from source documents, should be consistent with the source documents (or the discrepancies should be explained).

18.3 RISK/BENEFIT

IMM-101, in pancreatic cancer studies (IMM-101-002, IMM-101-002A) has been shown, when co-administered with gemcitabine, to provide clinically relevant survival benefits and improvements in progression free survival. The safety data indicated that this was achieved without significant additional toxicity. As such the risk/benefit for further evaluation in other cancer indications is favourable. The single most notable risk across all studies is that the subject may develop a site reaction to the injection that may on occasion prove troublesome. However there have been no instances where this has resulted in a need to stop treatment but rather has resulted in the need for a dose reduction or dose delay in a few instances. IMM-101 is therefore considered to have a favourable risk/benefit profile.

18.4 ELECTRONIC CASE REPORT FORMS

This study will use an eCRF. All relevant site staff will be trained on the eCRF and a reference manual will be provided. There will also be a helpdesk for sites to contact if they have any problems with using the eCRF system. The clinical monitor will review the eCRFs for completeness and adherence to the Protocol.

18.5 SOURCE DATA

Source documents (including all demographic and medical information, and an original of the signed informed consent form [ICF] indicating the study number and title) for each patient in the study will be maintained by the Investigator or designee (generally in the patient's files), and all information in the eCRFs must be traceable to the source documents.

All data must be recorded directly into the patient's medical record as source data. It will be confirmed at the study initiation monitoring visit which documents will be considered as source data for the Investigator site. These will be documented and reviewed by the monitor at each monitoring visit.

Source documents must be available to document the existence of the patient and substantiate the integrity of study data collected.

18.6 SAFETY DATA REVIEW COMMITTEE

An internal safety review committee will review the clinical safety data every 6 months

18.7 TERMINATION OF STUDY

18.7.1 Regular Termination of Study

The study will continue until all patients have had the opportunity of 18 months treatment on study.

The end of this study is defined as the date of the last visit of the last patient undergoing this study. In the event that the last patient in the study dies before their last visit, the study completion will be the date that Immodulon was notified of the death. Within 90 days of the end of the clinical study, the Sponsor will notify the Independent Ethics Committee (IEC) and regulatory authorities of the planned termination of the study as required according to national laws and regulations. If the study has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

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 post study completion or in the event of withdrawal from the study. This data will be collected until database lock.

18.7.2 Premature Termination of Study

The study may be terminated prematurely for any reason and at any time by the Sponsor, IEC, a regulatory agency, or the Chief Investigator. A decision to prematurely terminate the study is binding on the Investigator. The IEC and regulatory authorities will be informed about the reason and date of termination according to the applicable laws and regulations.

The Sponsor reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator. A study site may also be discontinued by the Sponsor for significant deviations from the Protocol or due to difficulties experienced in running the study at that centre.

The Sponsor may terminate this study in one particular or several study centre(s) for one of the following reasons:

- Non-compliance with ICH GCP and/or regulatory requirements.
- Centre cannot recruit an adequate number of patients.
- False documentation in the eCRF, either deliberately or due to carelessness.
- Inadequate co-operation with the Sponsor or its representatives.
- The Investigator requests closure of his/her study centre

If the study is terminated prematurely in one or more study centres, all affected Investigators must inform their patients and take care of appropriate follow-up and further treatment of the patients.

19. REFERENCES

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20 APPENDICES

Appendix 1 Study Schedule of Assessments for Treatment Phase

Appendix 2 ECOG/WHO Performance Status Assessment

Appendix 3 Summary of Protocol Amendments

Appendix 4 Study Acknowledgement/Protocol Signature Page

Appendix 1 Study Schedule of Assessments

	Screening*	Treatment Phase**																				
Week	**-21 to -1 days**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Visit window (± days)		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent	✓																					
Inclusion/Exclusion Criteria	✓	✓[1]																				
Demography & Baseline Disease History/Status	✓																					
Complete Medical History	✓																					
Physical Examination	✓	✓[2]	✓	✓		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓
Vital Signs and Weight	✓	✓[3]	✓	✓		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓
Safety Laboratory Evaluation [4]	✓	✓[2]	✓	✓		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓
CT Scan/MRI scan – Cohort A [5]	✓							✓				✓				✓				✓		
CT Scan/MRI scan – Cohort B [5]	✓				✓				✓				✓				✓				✓	
Serum Pregnancy Test [6]	✓																					
Hepatitis B and C [7]	✓																					
ECOG/WHO Performance Status	✓	✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
12-lead ECG	✓																					
Biopsy for PD-L1 assessment - Cohort A [8]	✓																					
BRAF Testing [9]	✓																					
Blood sample for immunological marker assessment - Cohort A	✓			✓		✓		✓				✓				✓				✓		
Blood sample for immunological marker assessment - Cohort B	✓				✓				✓				✓				✓				✓	
Biopsy sample for immunological marker assessment [10]	✓							✓														
IMM-101 Administration [11]		✓[3]	✓	✓		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓
Nivolumab Administration [11] [12]***		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Injection Site Reactions [13]			✓	✓		✓	✓	✓		✓		✓		✓		✓		✓		✓		✓
Prior/Concomitant Therapy including radiotherapy and surgery and procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Reporting	✓[16]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Treatment Phase																			
Week	**42**	**44**	**46**	**48**	**50**	**52**	**54**	**56**	**58**	**60**	**62**	**64**	**66**	**68**	**70**	**72**	**74**	**76**	**78**	**End of Study Visit** [14]
Visit	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	
Visit window (± days)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7
Physical Examination		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Vital Signs and Weight		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Safety Laboratory Evaluation [4]		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
CT Scan/MRI scan – Cohort A [5]		✓				✓				✓				✓				✓		✓[15]
CT Scan/MRI scan – Cohort B [5]			✓				✓				✓				✓				✓	✓[15]
ECOG/WHO Performance Status		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
12-lead ECG																				✓
Blood sample for immunological marker assessment - Cohort A		✓				✓														
Blood sample for immunological marker assessment - Cohort B			✓																	
Biopsy sample for immunological marker assessment																				
IMM-101 Administration [10]		✓		✓		✓		✓		✓		✓		✓		✓		✓		
Nivolumab Administration [11]***	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	[17]
Injection Site Reactions [12]		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓
Prior/Concomitant Therapy including radiotherapy and surgery and procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Reporting	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

* If felt to be appropriate by the investigator, some of the screening procedures may take place on the same day as enrolment into the study provided all results applicable for eligibility are available for review prior to enrolment.

** Study assessments may take place one day before the visit day when dosing is performed.

*** If a 4 weekly nivolumab dosing regimen is chosen by the investigator then the study visit will not be required (unless clinically indicated) on the 'redundant' nivolumab dosing days when no other study procedures are due to take place i.e. week 6 (Cohort A only), week 14 (Cohort A only), week 18, week 22 (Cohort A only), week 26, week 30 (Cohort A only), week 34, week 38 (Cohort A only), week 42, week 46 (Cohort A only), week 50, week 54 (Cohort A only), week 58, week 62 (Cohort A only), week 66, week 70 (Cohort A only), week 74, week 78 (Cohort A only).

1 Inclusion/exclusion criteria will be assessed during screening and confirmed before commencing any study treatment.

2 Only to be repeated if more than 7 days have elapsed since screening assessment.

3 The first dose of IMM-101 administered to each patient in the study should be followed by vital signs monitoring for at least 2 hours under medical supervision with resuscitation facilities available as a precautionary measure.

4 Includes haematology and clinical chemistry. These results should be available before dosing with IMM-101 so the blood samples may be taken the day before the scheduled visit to allow for this. Urinalysis is performed at Screening only.

5 Patient to have baseline CT or MRI scan within 21 days prior to visit 1. CT scans are then every 8 weeks (±7 days) from week 12 (Cohort A) or from week 6 (Cohort B) onwards or when clinically indicated, at the discretion of the investigator. At the discretion of the investigator, the frequency of scans may be increased to every 12 weeks (±7 days) for patients who continue on study beyond week 52. Imaging should follow calendar days and not be adjusted for any delays in treatment. Patients with an objective response should have a repeat scan after 4 weeks to confirm the response. Patients who obtain a confirmation scan do not need to undergo scheduled imaging assessment 4 weeks later.

6 In female patients of childbearing potential only. This test must be within 72 hours prior to first dose of IMM-101. If there is concern that the patient may be pregnant at any time during the study, then a repeat pregnancy test should be performed.

7 Performed during screening unless patient has a history of Hepatitis B or C, in which case they are ineligible.

8 Patient has a tumour sample (archived tissue in the last 3 months or newly obtained biopsy) that is adequate for PD-L1 assessment prior to enrolment. The tumour sample will be collected during screening for PD-L1 expression testing from all patients in Cohort A. Patients will be eligible to participate regardless of the level of PD-L1 expression. Patients with an inadequate archived sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator.

9 Performed during screening unless patient has documented BRAF status.

10 Cohort A - Baseline sample for PD-L1 testing is used for baseline immunological testing. Archived tissue collected during the 3 months prior to Screening may be used if available. Samples for Cohort A and Cohort B are subject to consent for immunological testing. Subsequent sample will be scheduled at Week 12 (to be taken in the following 2 weeks) for Cohort A. Subsequent sample requested from Cohort B only if a response to treatment is recorded.

11 If IMM-101 and nivolumab are due to be administered on the same day, IMM-101 will be given before nivolumab.

12 According to Investigator choice, Nivolumab will be given as 3mg/kg IV infusion every two weeks, 240mg IV infusion every two weeks or 480mg IV infusion every four weeks.

13 Injection site reactions are recorded prior to each new injection and at the End of Study visit.

14 When a patient withdraws from, or completes, the study, where possible the patient should attend an EOS visit. This visit should be within 28±7 days after the final study dose of IMM-101. If an end of study visit is not possible any unresolved adverse events and update on concomitant medications should be followed up by other means of contact (e.g. telephone; Section 9.5). Patients will then be followed up for survival.

15 A CT scan is only required at End of Study visit if there is more than 8 weeks elapsed since the last scan (or more than 12 weeks elapsed if last scan was after week 52) and, in both cases, when there is no documented progression.

16 From time of signing informed consent.

17 Any patients in Cohort A continuing treatment with nivolumab off-study should have their End of Study visit before they receive this.

Additional Schedule for Patients in Cohort B who receive Ipilimumab alongside IMM-101 after discontinuing nivolumab either because they continue to progress on study according to RECIST 1.1 and/or investigator decision that continuing to receive nivolumab is no longer appropriate due to clinical progression. Assessments below are <u>in addition</u> to those listed in the main Schedule of Assessments above.

Week	Week X – 2 weeks	Week X – 1 week	Decision to start patient on ipilimumab (Week X)	Week X + 1 week	Week X + 2 weeks	Week X + 3 weeks	Week X + 4 weeks	Week X + 5 weeks	Week X + 6 weeks	Week X + 7 weeks	Week X + 8 weeks	Week X + 9 weeks	Week X + 10 weeks	Week X + 11 weeks	Week X + 12 weeks
Ipilimumab Administration (Cohort B only, if considered appropriate by investigator) [1] [2] [3]			✓			✓			✓			✓[4]			
IMM-101 Administration [4]	✓[5]				✓				✓				✓		
Nivolumab Administration [2]	✓														
Prior/Concomitant Therapy including radiotherapy and surgery and procedures	✓	✓	✓			✓			✓	✓		✓		✓	
Adverse Event Reporting	✓	✓	✓			✓			✓	✓		✓		✓	

1. In the event of toxicity, doses may be delayed, but all ipilimumab doses must be administered within 16 weeks of the first dose First dose of ipilimumab can start at any time during the study but must be at least 2 weeks after last dose of nivolumab and should not be taken together with nivolumab.
2. Ipilimumab will be given as a 3 mg/kg IV infusion over 90 minutes every three weeks for a maximum of 4 doses.
3. If IMM-101 and ipilimumab are due to be administered on the same day, IMM-101 will be given before ipilimumab.
4. Patients in cohort B who receive all 4 doses of ipilimumab should remain on study after this time and follow the protocol assessments. They may continue to receive IMM-101 during this period until unacceptable side-effects, the investigator's decision to discontinue treatment, withdrawal of patient consent or 18 months of IMM-101 treatment, whichever is the sooner.
5. Schedule to be adjusted dependent on time of last IMM-101 dose to maintain the dose interval per protocol.

Appendix 2 ECOG/WHO Performance Status Assessment

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

Grade	
0	Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5	Death

Appendix 3 Summary of Protocol Amendments

Protocol Amendment 1

This protocol amendment, dated 16 December 2019, addressed the following changes to the study protocol (Final version 1.0, 9 April 2018):

- Removal of the exclusion criterion that limits the number of treatment regimes allowed prior to anti-PD-1 therapy to one, for patients enrolling in Cohort B of the study.
- Amendment of the inclusion criterion that specifies the number of doses of prior treatment with anti-PD-1 therapy that are required for Cohort B of the study.
- Amendment of dosing schedule of nivolumab to accommodate an investigator choice between 3mg/kg 2 weekly, 240 mg 2 weekly or 480mg 4 weekly.
- Change of time between end of other investigational product and first study dose from 4 weeks to 3 weeks.
- Clarification that the biopsy sample used for PD-L1 testing at Screening is the same as that used for immunological marker testing for Cohort A of the study.
- Confirmation that study assessments, as well as blood samples, may be taken the day before a scheduled dosing day.
- Inclusion of final data from the IMM-101-008 study.
- Clarification that an end of study visit should be carried out, if possible, following completion or early termination. Should this not be possible, unresolved adverse events should still be followed up.
- Clarification of assessment of response.
- Addition of more sites.
- Clarification of disease control rate.
- Clarification of sub-groups for analysis.
- Correction of error in survival rates quoted.
- Correction to Investigator Statement.
- Addition of Summary of Protocol Amendments into the appendices.
- Correction of minor typographical errors (not individually listed).

This Protocol Amendment is considered **substantial**.

Appendix 4 Study Acknowledgement/Protocol Signature Page

STUDY ACKNOWLEDGEMENT/PROTOCOL SIGNATURE PAGE

Investigator's Statement:

I have read and understand the foregoing Protocol entitled "A Study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor Therapy in Patients with Advanced Melanoma", study number IMM-101-015, EudraCT No. 2018-001346-34 and agree to conduct the Study, in compliance with Good Clinical Practice (CPMP/ICH/135/95) as amended, designated Standard Operating Procedures, National Laws and regulations of the countries conducting the study and within the principles of the Declaration of Helsinki as amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Investigator's Name (please print)	Investigator's Title
Date (dd-mmm-yyyy)	Investigator's Signature