Final Study Protocol for:

Study IMM-101-008

NCT01559818

A Long Term Follow up Study for Patients Who Previously Took Part in the Phase I Study IMM-101-001

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE: An Open Label Long-term Follow-up Study for Patients with Melanoma who were Previously Enrolled in the Phase I Study IMM-101-001

PROTOCOL NUMBER: IMM-101-008

EUDRACT NUMBER: 2011-003967-31

DRUG: IMM-101

SPONSOR: Immodulon Therapeutics Limited

6-9 Stockley Park
Uxbridge
UB11 1FW
United Kingdom

CHIEF INVESTIGATOR: Professor Angus Dalgleish
St George's University of London
Cranmer Terrace
London
SW17 0RE
United Kingdom

VERSION TABLE

Version 1.0	15th September2011
Version 2.0 incorporating Amendment No. 1.0	21st November 2011
Version 3.0 incorporating Amendment No. 2.0	13th February 2012
Version 4.0 incorporating Amendment No. 3.0	1st July 2012
Version 5.0 incorporating Amendment No. 4.0	1st November 2013
Version 6.0 incorporating Amendment No 5.0	28 July 2014
Version 7.0 incorporating Amendment No 6.0	7 November 2014
Version 8.0 incorporating Amendment No 7.0	05 June 2015

STATEMENT OF CONFIDENTIALITY

SIGNATURE PAGE

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

This protocol is approved by:

Professor Angus Dalgleish Chief Investigator St Georges University of London	Signature	Date
Frances MacIntosh Medical Advisor Immodulon Therapeutics Ltd	FM MacIntosh	8th June 2015
	Signature	Date

SIGNATURE PAGE

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

This protocol is approved by:

Professor Angus Dalgleish Chief Investigator St Georges University of London	Signature	8/6/2015 Date
Frances MacIntosh Medical Advisor Immodulon Therapeutics Ltd	Signature	Date

CONTACT DETAILS

SPONSOR:	Immodulon Therapeutics Ltd. 6-9 The Square, Stockley Park, Uxbridge, UB11 1FW United Kingdom (UK) Tel: +44 (0) 208 929 9282 Fax: +44 (0) 208 929 9283
MEDICAL MONITOR	Immodulon Therapeutics Ltd. 6-9 The Square, Stockley Park, Uxbridge, UB11 1FW United Kingdom (UK) Tel: +44 (0) 208 929 9282 Fax: +44 (0) 208 9299283
OUT OF HOURS MEDICAL COVER:	020 3137 8172
CHIEF INVESTIGATOR:	Professor Angus Dalgleish Foundation Professor of Oncology St George's University of London Cranmer Terrace, London, SW17 0RE UK Tel.: +44 (0) 20 8725 0809 Fax: +44 (0) 20 8725 0158 Email: dalgleis@sgul.ac.uk
SERIOUS ADVERSE EVENT CONTACT DETAILS:	Emas Ltd. 71 Knowl Piece, Wilbury Way, Hitchin Hertfordshire, SG4 0TY Tel.: +44 (0) 1462 422717 Fax: +44 (0) 1462 600456 Email: Drug.Safety@emas-medical.com

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

TABLE OF CONTENTS

1. GLOSSARY

ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
BCG	Bacille Calmette-Guérin vaccine; a preparation of attenuated live *Mycobacterium bovis*
BRM	Biological Response Modifiers
CPMP	Committee for Proprietary Medicinal Products
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computerised Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DTH	Delayed-Type Hypersensitivity: A cell-mediated immune response that peaks 24 to 72 hours after stimulation with an antigen to which the body has previously been exposed; in an antigen skin test, a local DTH reaction characterized by redness and induration (hardness and swelling) indicates past exposure
ECG	Electrocardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials is the European Clinical Trials Database of all clinical trials commencing in the European Union from 1 May 2004 onwards
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-α	Interferon-alpha
IMM-101	Suspension of heat-killed whole cell *Mycobacterium obuense*
IUD	Intrauterine Device
MCB	Master Cell Bank
MHRA	Medicines and Healthcare products Regulatory Agency
M. obuense	*Mycobacterium obuense*
MRI	Magnetic Resonance Imaging
M. vaccae	*Mycobacterium vaccae*

N	Number (of patients)
NCI	National Cancer Institute
NCTC	National Collection of Type Cultures
NK	Natural Killer Cells
OS	Overall Survival
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th_2	T helper 2 cells
UK	United Kingdom
WHO	World Health Organisation
WMA	World Medical Association

2. PROTOCOL SYNOPSIS

Title	An open label long term follow up study of patients with melanoma who were previously enrolled in the Phase I study IMM-101-001
Protocol Number	IMM-101-008
EudraCT Number	2011-003967-31
Investigational Product	IMM-101: A suspension, in borate-buffered saline, of heat-killed whole cell *Mycobacterium obuense* for intradermal injection.
Chief Investigator	Professor Angus Dalgleish St George's University of London Cranmer Terrace London, SW17 0RE, United Kingdom (UK)
Number of Sites	Two, The London Clinic, Advanced Therapies Centre, London, UK and St George's Hospital, London, UK
Phase	Long term follow up following a Phase I study
Indication	Melanoma
Study Design	Patients who were previously enrolled in Study IMM-101-001 and who provide informed consent will be eligible to participate in this study. Once eligibility is confirmed, a full medical history covering the period from their completion of Study IMM-101-001 to date will be taken. The patient will then enter the Treatment Phase of the study and follow the Study Flow Chart of Assessments (Appendix 1).
Objectives	• To determine the long term safety profile of IMM-101 administered intradermally for extended use • To document the clinical course of the patients previously enrolled in Study IMM-101-001. • To monitor selected markers of tumour burden and immunological status.
Study Duration	Patients will continue until death or withdrawal. In the case of withdrawal, separate consent will be sought to allow the continued collection on patient status.
Sample Size	Surviving patients from the IMM-101-001 protocol (EudraCT number: 2009-012447-42) will be invited to enrol in the study.
Principal Selection Criteria	Patients are eligible to be included in the study if they: 1. Were previously enrolled in Study IMM-101-001 2. Consent to make their disease and treatment history for the intervening period between their completion of Study IMM-101-001 and enrolment in this study available to the Sponsor 3. Give signed informed consent for participation in the study Patients will be ineligible if one or more of the following statements are applicable:

	1. Female patient of child-bearing potential who is not, in the opinion of the Investigator, using an approved method of birth control (e.g., physical barrier [patient and partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device [IUD]). Those patients that utilise hormonal contraceptives must have used the same method for at least three months before additional barrier contraception (as described above) is discontinued from being used concomitantly with the hormonal contraception. Patient of non-child-bearing potential are defined as having 12 month amenorrhoea or are surgically sterile. 2. Female patient who is pregnant, breast feeding or planning a pregnancy during the course of the study. A pre-treatment urine pregnancy test measuring human chorionic gonadotrophin (hCG) must be negative. 3. Patient is unable or unwilling to comply with the protocol.
Investigational Product Formulation Dosage Administration	IMM-101, a suspension of heat-killed whole cell *M. obuense* in borate-buffered saline. IMM-101 10 mg/mL will be provided either as a 0.3 mL volume in a 1 mL single use vial or a 2.0 mL volume in a 4 mL single use vial. A single 0.1 mL intradermal injection of IMM-101 (10 mg/mL). The treatment regimen with IMM-101 will be one dose given every 4 weeks or as close to this interval as permitted due to practical or logistic considerations. The dose given and/or the interval may be modified at the discretion of the Investigator provided the minimum period between doses is no less than 14 days. If the dosing interval is increased, the patient should still attend the study site for safety assessments preferably every 3 months but, if this is not possible, every 6 months at a minimum. IMM-101 is given via intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose.
Endpoints Safety	• Local injection site tolerability • Adverse Events.
Efficacy	• Overall survival (OS) • Reduction in metastatic disease
Exploratory	Blood samples will be collected and sera prepared for analysis of immunological markers and mediators. Exploratory endpoints may include a change in one or more markers of immune status based on cellular involvement, function or cytokine/immune mediator production such as, for example, cytokines and antibodies, or any other clinically or immunologically relevant assays that may become pertinent during the course of the long-term follow up. Note: Exploratory endpoints will be specified in a separate laboratory manual and will be reported separately to the main safety and tolerability endpoints of the study.
Statistical Methods	Descriptive summary of the results of the study will be provided along with full listings. No formal analysis of the results is anticipated.

3. BACKGROUND INFORMATION

The proposed study will explore the long term safety and tolerability of continued administration of IMM-101 in patients who were previously enrolled in the Phase I safety and tolerability study IMM-101-001.

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 characterized 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. Results are presented in Section 3.3.

It has been shown that, following administration of various cancer vaccines, delayed-type hypersensitivity (DTH) is a significant and independent predictor of survival in cancer patients. Although this finding has been inconsistent it may reflect mechanistic variation rather than a spurious correlation. If localised inflammation is reflective of a generalised immune activation, this may in turn indicate an increase in anti-tumour immune responses.

IMM-101 has effects on the immune system which are hypothesised to be beneficial to this patient population:

- Induction of innate and Type I immunity with promotion of cell-mediated cytotoxicity.
- Induction of immunoregulation which should help to control the adverse effects of chronic inflammation or inappropriate $T_{effector}$ activity (Th_2 biased) at the site of the tumour.

3.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

IMM-101 is a suspension of heat-killed whole cell *Mycobacterium obuense* in borate-buffered saline, produced to Good Manufacturing Practice (GMP) for intradermal administration to humans.

3.2 NON-CLINICAL FINDINGS

Preliminary work *in vitro* has been carried out to investigate effects of exposure to *M. obuense* on cellular and molecular markers of immune status in human whole blood cells. Guinea pig sensitisation assays confirming similar local reactivity to that induced with the related organism *M. vaccae* 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.

Further details can be found in the Investigator's Brochure (1).

3.3 CLINICAL FINDINGS

Study Number IMM-101-001: This was an 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.

A total of 19 patients were enrolled into the study between 10 March 2010 and 27 July 2010, and the study was completed by 23 September 2010; six patients received placebo followed by 3 doses of IMM-101 0.1 mg, six patients received placebo followed by 3 doses of

IMM-101 0.5 mg, and six patients received placebo followed by 3 doses of IMM-101 1.0 mg, over a 4 week period. One patient received placebo followed by 2 doses of IMM-101 0.5 mg but was withdrawn after the second dose of IMM-101 as they were found retrospectively to have been ineligible at study entry due to brain metastases; an additional patient was recruited to this dose cohort to ensure data on six patients were collected.

The placebo injection was administered on Day -3 and the IMM-101 injections over a 4-week period (Day 0, 14 and 28). All injections were administered intradermally. At each dosing level, one patient was administered IMM-101 at least 24 hours in advance of the remaining patients in order to review safety evaluations and observe local injection site reactions. The decision to dose-escalate was preceded by a comprehensive review of safety data from the previous dose cohort.

There were no dose limiting toxicities observed and no evidence to suggest a clinically significant impact upon haematological indices, biochemical parameters or cardiac function. All documented changes in vital signs from screening to end of study were unremarkable.

There were no treatment-emergent adverse events (AEs) reported in the period following the placebo injection and before the first dose of IMM-101 – thus allowing a clear definition of the tolerability of the test product.

Eighteen patients (95%) reported at least one treatment-emergent AE after receiving IMM-101. Over the course of the study, a total of 119 treatment-emergent AEs were reported. There were 86 reports of treatment-emergent AEs that would be accepted as typical of a post-vaccination state (such as injection site reactions, joint pains/aches, headaches and flu-like symptoms) occurring at all dose levels. These were mainly mild in intensity, mostly resolved in a matter of days and responded well to simple supportive medication (e.g. paracetamol). They were entirely consistent with the pooled information available on *M. vaccae*, a closely related organism, and were generally less intense than symptoms typically observed following Bacille Calmette-Guérin (BCG) vaccination of tuberculin negative individuals.

Sixteen patients (84%) reported at least one treatment-related AE. A total of 56 treatment-related events were reported; the most frequently reported treatment-related adverse events were in the 'administration site conditions' category. All these injection reactions (local swelling, pain, erythema and occasionally mild ulceration) were considered 'non-serious' by the Investigator; no patient withdrew due to an intolerable injection site reaction.

Only one serious adverse event (SAE) was reported; one patient in the IMM-101 0.5 mg group was hospitalised with progressive shortness of breath and found to have progressive disease (metastatic lung lesion). The SAE was reported to be unrelated to IMM-101 by the Investigator.

The data collected at site to document and characterise injection site reactions indicated a trend for resolution over time, with the earlier and older skin reactions appearing reduced in size compared to the more recent ones at the end of the study. Furthermore, it appears that repeated administration does not predispose the patient towards larger or more intense reactions after subsequent administrations.

In summary, the study was conducted per protocol and provided considerable knowledge concerning the administration of IMM-101 and management of any side-effects. The AEs observed so far with IMM-101 are in line with expectations, are manageable and are in keeping with data from non-clinical models and past experience in humans with similar whole cell mycobacterial preparations. The injection site reactions are consistent for this

class of product and are well tolerated by the patients. Local skin reactions should be viewed as a normal and predicted reaction to exposure to a preparation of mycobacterial antigens.

3.4 POTENTIAL RISKS AND BENEFITS

The main risk associated with the administration of IMM-101 is the development of injection site reactions. The observed profile of adverse events is in line with expectations, is manageable and is in keeping with data from non-clinical models and past experience in humans treated with similar whole cell mycobacterial preparations. The injection site reactions are consistent for this class of product and have been well tolerated by these patients to date both in the context of the Phase I study and following subsequent multiple administrations on a named patient basis.

No safety concerns were evident in the Phase 1 study. However, there was only relatively limited patient exposure to IMM-101 with each patient receiving just 3 doses on study. There is the potential risk that repeated administration of IMM-101 may result in an increase in the injection site reactions. This risk will be carefully managed through close Investigator supervision and the obligation to reduce the dose, delay administration or withdraw the patient from the study in the presence of unexpectedly severe or long-lasting site reactions.

In light of the ”3E‘s” hypothesis of cancer (Elimination, Equilibrium and Escape) (2), continued treatment with IMM-101 could have the beneficial effect of, if not inducing “Elimination”, of prolonging or helping to restore the “Equilibrium” mode, which should be a clinically acceptable situation. While a potential benefit from participation in this study cannot be ruled out, the study is not designed to provide evidence for the potential therapeutic efficacy of IMM-101.

3.5 TREATMENT

IMM-101 is a suspension of heat-killed whole cell *M. obuense* sourced from the National Collection of Type Cultures (NCTC) with reference NCTC 13365 and produced in accordance with GMP.

The treatment regimen with IMM-101 will be one dose given every 4 weeks or as close to this interval as permitted due to practical or logistic considerations. The dose interval may be modified at the discretion of the Investigator provided the minimum period between doses in no less than 14 days. If the dosing interval is increased, the patient should still attend the study site for safety assessments preferably every 3 months but, if this is not possible, every 6 months at a minimum.

IMM-101 (10 mg/mL) will be administered as a single 0.1 mL intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose. In the event of unacceptable local reaction, the dose of IMM-101 may be reduced or the dosing interval prolonged at the discretion of the Investigator.

3.6 CONDUCT OF STUDY

This clinical study will be conducted in compliance with this Protocol, the current version of the guidelines of the World Medical Association Declaration of Helsinki as revised, the ICH Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95), designated standard operating procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents in the United Kingdom.

3.7 POPULATION

All surviving patients from the IMM-101-001 protocol (EudraCT number: 2009-012447-42) will be invited to enrol in the study by the Principal Investigator.

4. STUDY OBJECTIVES AND PURPOSE

4.1 OBJECTIVES

The objectives for this study are:

a) to determine the long term safety profile of IMM-101 administered intradermally for extended use

b) to document the long term clinical course of the patients previously enrolled in Study IMM-101-001

c) to monitor selected markers of tumour burden and immunological status.

4.2 RATIONALE

No safety concerns were evident in the previous Phase 1 study which these patients all participated in, however, there was only relatively limited patient exposure to IMM-101 in the context of the study with each patient receiving just 3 doses on study.

All 18 eligible patients had completed the study by the end of September 2010 and the majority continued to receive IMM-101 on a named patient basis under the supervision of the Chief Investigator. As of August 2011, a number of patients have stopped treatment (3 died, 1 stopped due to pregnancy and 2 for unknown reasons). All remaining patients have expressed a wish to continue to receive treatment and the Chief Investigator has confirmed that they consider it in these patients' best interest to do so.

The Sponsor considers it more appropriate to continue treatment of this cohort of patients in the context of a formal long term follow up safety study rather than on a named patient basis so that the patients can be followed for long term safety.

5. INVESTIGATIONAL PLAN

5.1 ENDPOINTS

5.1.1 Safety and Tolerability

- Local and systemic toxicities.
- Adverse Events with documentation of number, type and degree of toxicities as measured by the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 [5] where appropriate.

5.1.2 Efficacy

- Overall survival (OS).
- Reduction in metastatic disease.

5.1.3 Exploratory

Blood samples will be collected and sera prepared for analysis of immunological markers and mediators.

Exploratory endpoints may include a change in one or more markers of immune status based on cellular involvement, function or cytokine/immune mediator production such as, for example, cytokines and antibodies, or any other clinically or immunologically relevant assays that may become pertinent during the course of the clinical trial.

Note: Exploratory endpoints will be specified in a separate laboratory manual and will be reported separately to the main safety, tolerability and efficacy endpoints of the study.

5.2 OVERALL STUDY DESIGN AND PLAN

This is an open-label long term follow up study. The study will consist of two phases:

1. Screening and enrolment

   Patients, who provide informed consent, will participate in a screening period of up to 28 days to establish eligibility. Once eligibility is confirmed a full disease and treatment history covering the period from their completion of Study IMM-101-001 to date will be taken.

2. Treatment

   Patients can receive ongoing treatment every 4 weeks or as close to this interval as permitted due to practical or logistic considerations until death or withdrawal, unless such therapy is contraindicated, the patient does not wish to continue or the study is terminated by the Sponsor. At no point should the elapsed period between IMM-101 doses be less than 14 days. The Study Flow Chart of Assessments is provided as Appendix 1.

Patients may choose to withdraw from the study at any time and for any reason. IMM-101 should be stopped or the dosing regimen reduced if felt to be necessary by the Investigator and/or patient (e.g., intolerable injection site reactions). In the event of an injection site reaction of Grade 3 and above, and/or if significant ulceration, tenderness or lymphadenopathy is observed, at the discretion of the Investigator, patients may be administered a half dose of the study drug (i.e., a single 0.05 mL intradermal injection of IMM-101) or the timing of the injection may be delayed. If the dosing interval is increased, the patient should still attend the study site for safety assessments preferably every 3 months but, if this is not possible, every 6 months at a minimum. In addition, if the patient does not attend the clinic for a study visit within a calendar month, the clinic will telephone the patient to enquire about injection site reactions, adverse events, concomitant medications and any other concerns. Details of the call will be recorded in the patient notes with appropriate information on adverse events and concomitant medications also being recorded in the CRF. The blood sample for exploratory analysis should continue to be taken every 6 months.

Any change in the dose of study drug administered or the frequency of dose administration should be recorded in the patient's case report form (CRF). In the case of withdrawal, separate consent will be sought to allow the continued collection on patient status.

5.2.1 Study Procedures

5.2.1.1 Screening and Enrolment (Day -28 to Day 0)

Patients will complete the screening assessments within 28 days of admission to the study, 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 general practitioner (GP) will be informed in writing about the participation of their 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 on a "Patient Screening Log".

The following procedures and assessments will be conducted during the screening phase and recorded in the patient's CRF:

- Informed consent.
- Patient eligibility (inclusion/exclusion criteria).
- Demographics and baseline data (gender, date of birth, race, height and presence of pre-existing injection site reactions).
- Best effort must be made to document disease and treatment history including during the period since completion of Study IMM-101-001.
- Documentation of any concurrent illnesses.
- Documentation of date of last dose of IMM-101.
- Document results and record date of last computerised tomography (CT) scan.
- Record the most recent report of disease staging.
- Urine pregnancy test if applicable.
- Both male and female patients should be instructed to use adequate contraception whilst taking part in the study.
- WHO performance status (see Appendix 2).
- Any prior/concomitant therapy/medications (taken up to 2 weeks before screening).
- AE/SAE reporting (from the time of signing informed consent).

5.2.1.2 Treatment Phase

Day 0

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

- Re-check the patient's eligibility (i.e., inclusion and exclusion criteria).
- Re-check that at least 14-days have elapsed since the last dose of IMM-101 given as part of the named patient program.
- Blood samples for exploratory endpoints.
- Assess pre-existing injection site reactions.
- IMM-101 administration (intradermal injection).
- Any concomitant medications.
- AE/SAE reporting.

Subsequent Visits at nominal 4 week intervals

- Check that at least 14-days have elapsed since the last dose of IMM-101.

- Assess injection site reactions.
- Any concomitant medications.
- AE/SAE reporting.
- IMM-101 administration (intradermal injection).

Nominally Week 24, 48, 72 and 96 (i.e., approximately every 6 months until death or withdrawal)

In addition to the assessments outlined above which are to be conducted at every visit a blood sample will be taken for exploratory endpoints.

5.3 STUDY TREATMENT

5.3.1 Identity of Investigational Product

The strain of *M. obuense* used to produce IMM-101 was sourced from the NCTC and is a stable 'rough variant' strain. IMM-101 is produced by conventional culturing techniques, from the source culture *M. obuense* NCTC 13365, from which a master cell bank (MCB) has been created. Following growth under controlled conditions, the harvested organisms are heat-killed (by autoclaving) and formulated at a concentration of 50 mg (wet weight) per mL, as a suspension in borate-buffered saline, pH 7.7-8.3. This bulk product is then further diluted with borate-buffered saline to 10 mg/mL under aseptic conditions. The final product is presented as a fine suspension in borate-buffered saline, pH 7.7-8.3, in single use 1.0 mL capacity glass vials, each containing 0.3 mL or single use 4.0 mL capacity glass vials, each containing 2.0 mL. The suspension is turbid, containing yellow-orange particles that settle to the bottom of the vial on standing and are easily re-suspended with gentle shaking.

Primary manufacture is undertaken to GMP standards at BioElpida, Dardilly, 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.

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

5.3.2 Packaging and Labelling

The study drug will be labelled in English. The label will contain the information as required by the MHRA.

Labelling will be performed according to Annex 13 of the GMP guidelines of the European Commission, ICH-GCP guidelines, and local law.

5.3.3 Storage

The study drug 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. After the product has been removed from the fridge it must be allowed to equilibrate for 5 to 10 minutes before being used. The product must be used within 6 hours of being removed from the fridge or it should be discarded.

Study drug 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 the study drug.

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

5.3.4 Destruction of Surplus Medication

All surplus study drug will be sent for destruction following authorisation from the Sponsor.

5.4 DURATION OF STUDY PARTICIPATION

Patients can receive ongoing treatment every 4 weeks or as close to this interval as permitted due to practical or logistic considerations until death or withdrawal, unless such therapy is contraindicated, the patient does not wish to continue, or the study is terminated by the Sponsor.

5.5 DISCONTINUATION CRITERIA

The discontinuation criteria for individual patient and/or the entire study are presented in Section 6.3.

5.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

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

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

5.7 CODE BREAKS

Not applicable.

5.8 SOURCE DATA

Source documents (including all demographic and medical information, CRFs, 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 CRFs must be traceable to the source documents.

All data should be recorded directly into the patient's medical record as source data. It will be confirmed at the Trial Initiation Monitoring Visit which documents will be considered as

source data for the Investigator centre. 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.

5.9 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Not Applicable

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1 PATIENT INCLUSION CRITERIA

Patients are eligible to be included in the study if they:

1. Were previously enrolled in Study IMM-101-001.
2. Give consent to make their disease and treament history for the intervening period between their completion of Study IMM-101-001 and enrolment in this study available to the Sponsor.
3. Give signed informed consent for participation in the study.

6.2 PATIENT EXCLUSION CRITERIA

Patients will be ineligible if one or more of the following statements are applicable:

1. Female patient of child-bearing potential who is not, in the opinion of the Investigator, using an approved method of birth control (e.g., physical barrier [patient and partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device [IUD]). Those patients that utilise hormonal contraceptives must have used the same method for at least three months before additional barrier contraception (as described above) is discontinued from being used concomitantly with the hormonal contraception. . Patient of non-child-bearing potential are defined as having 12 month amenorrhoea or are surgically sterile.
2. Female patient who is pregnant, breast feeding or planning a pregnancy during the course of the study. A pre-treatment urine pregnancy test measuring human chorionic gonadotrophin (HCG) must be negative.
3. Patient is unable or unwilling to comply with the protocol.

6.3 PATIENT WITHDRAWAL CRITERIA

6.3.1 Removal of Patients from Therapy or Assessment

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.

In the event that the patient drops out of the study or is withdrawn from the study, the withdrawal page in the patient's CRF should be completed. On the withdrawal page the

Investigator (or designee) should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal.

The following are reasons for patient dropout/withdrawal:

Withdrawn by the Investigator due to:

- Adverse event.
- Protocol violation or non-compliance with the Protocol.
- Intolerable injection site reaction.
- Pregnancy.
- Toxicity.
- Other reasons.

Withdrawal requested by the patient due to:

- An AE for which the Investigator did not consider removal from the study necessary.
- Withdrawal of consent.
- Other.

Other:

- Lost to follow-up.
- Administrative problems.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data.

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary. In the case of withdrawal, separate consent will be sought to allow the continued collection on patient status.

6.3.2 Pregnancy

6.3.2.1 Female Patient's Pregnancy

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

Patients should 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.

Whenever possible a pregnancy should be followed to term, any premature terminations reported to Emas Drug Safety, 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.

6.3.2.2 Male Patient's Partner's Pregnancy

Male patients should be instructed to use adequate contraception whilst taking part in the study.

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

Whenever possible any pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to the Sponsor and/or Emas Drug Safety after delivery and at important developmental milestones during the first year.

6.4 TERMINATION OF STUDY

6.4.1 Regular Termination of Study

The end of this study is defined as the date of the last visit of the last patient undergoing this study. Within 90 days of the end of the clinical study, the Sponsor will notify the Independent Ethics Committee (IEC) and MHRA of the regular 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.

6.4.2 Premature Termination of Study

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

If the study is terminated prematurely, the Investigator must inform their patients and take care of appropriate follow-up and further treatment of the patients.

6.5 FURTHER TREATMENT AFTER THE END OF THE STUDY

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

7. TREATMENT OF PATIENTS

7.1 TREATMENTS ADMINISTERED

7.1.1 IMM-101

Formulation: IMM-101, a suspension of heat-killed whole cell *M. obuense* in borate-buffered saline.

IMM-101 will be provided either as a 0.3 mL volume in a 1 mL single use vial or as a 2.0 mL volume in a 4 mL single use vial. The batch(es) used in this study are comparable to that previously tested in pre-clinical safety studies and the previous Phase 1 study.

Note: The product is particulate and must be shaken gently before use to re-suspend the particulate matter.

Dosage: A single 0.1 mL intradermal injection of IMM-101 (10 mg/mL).

Administration: The treatment regimen with IMM-101 will be one dose given every 4 weeks or as close to this interval as permitted due to practical or logistic considerations. The dose interval may be modified at the discretion of the Investigator provided the minimum period between doses is no less than 14 days.

IMM-101 (10 mg/mL) will be administered as a single 0.1 mL intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose.

7.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Not Applicable.

7.3 SELECTION OF DOSES IN THE STUDY

A dosing schedule with IMM-101 which includes a period of induction, characterised by a series of administrations at close intervals followed by a maintenance phase with a single administration on a monthly basis has been proposed. It is believed that the period of induction will act by priming and boosting the patient's own immune system which, following a resting period during which anti-tumour immune responses can become established, would then require only periodic administrations or occasional boosting to maintain them.

The concept of priming and boosting has been used in other immunotherapeutic approaches to cancer with effective results. In a series of clinical investigations, Prostvac™, a prostate cancer immunotherapeutic regimen consisting of viral vectors containing transgenes for prostate-specific antigen and T cell co-stimulatory molecules, was administered in a primer step followed by multiple administrations as boosters [3, 4].

It is proposed that IMM-101 priming and boosting steps may stimulate both innate and adaptive immunity. It may act by rapidly activating cells of the innate immune system, including natural killer (NK) cells and macrophages, and through repeated stimulation it may elicit adaptive immune responses aimed at boosting anti-tumour responses. Compared to the immediacy of innate immune responses, adaptive immunity requires time to develop and may benefit from repeated stimulation to boost cellular involvement thereby eliciting more effective immune responses. Once fully established, adaptive immunity will only require regular administrations to maintain the responses.

The Phase I safety study was an intra-patient placebo-controlled study, to evaluate the safety and tolerability of 3 doses namely 0.1 mg (1 mg/ml), 0.5 mg (5 mg/ml), and 1.0 mg (10 mg/ml) of IMM-101. The dosing schedule was 3 doses of IMM-101 given at two-week intervals i.e. a period of induction or priming. In the intervening period between completing the Phase 1 study and enrolling onto this long term follow up study most patients will have been receiving IMM-101 at approximately four-week intervals, i.e., on a 'maintenance' cycle of one dose per month. It is proposed that this monthly maintenance cycle be continued in this long term study.

The proposed dose of IMM-101 is 1 mg/dose (0.1 mL of a 10 mg/mL solution) administered intradermally. Previous experience in the Phase I safety and tolerability study in patients with melanoma has suggested that this dose is safe and well tolerated. The skin reaction that develops at the site of injection is characterized by erythema, local swelling and occasionally mild ulceration. All symptoms are to be expected given the known pharmacology of the product and previous extensive clinical experience with the closely related organism *M. vaccae*. Furthermore data from this safety and tolerability study with IMM-101 has

revealed that skin reactions resolve satisfactorily over time and appear not to be exacerbated by either prior or subsequent administration of IMM-101.

7.4 SELECTION AND TIMING OF DOSE FOR EACH PATIENT

The treatment regimen with IMM-101 will be one dose given every 4 weeks or as close to this interval as permitted due to practical or logistic considerations. The dose interval may be modified at the discretion of the Investigator provided the minimum period between doses is no less than 14 days.

IMM-101 (10 mg/mL) will be administered as a single 0.1 mL intradermal injection into the skin overlying the deltoid muscle, with the arm being alternated between each dose.

7.5 DOSE ADJUSTMENT CRITERIA

There are no planned changes to the dose of the study drug.

There are no formal stopping criteria for IMM-101. Injection site reactions are expected and therefore it is important not to withhold IMM-101 but, if at all possible, to continue even if at a lower dose. IMM-101 should only be stopped if felt to be necessary by the Investigator and/or patient (e.g., intolerable injection site reactions). In the event of an injection site reaction of Grade 3 and above, at the discretion of the Investigator, patients may be administered a half dose of the study drug (i.e., a single 0.05 mL intradermal injection of IMM-101) or the time interval between doses may be increased. Any change in the dose of study drug or the frequency at which it is administered should be recorded in the patient's CRF.

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

7.6 CONCOMITANT MEDICATION

All concomitant medication taken during the study must be recorded in the CRF with indication, daily dose and dates of administration.

Any other medication that is considered necessary for the patient’s welfare, and which is not expected to interfere with the evaluation of the study drug may be given at the discretion of the Investigator.

There are no prohibited medications during this long term follow up study; however some medications should be used with caution when given concomitantly with IMM-101 as discussed below.

Cytokines (e.g., IFN-α), other cytotoxics, monoclonal antibodies, anti-tumour vaccines, or biological response modifiers (BRM) as well as chronically administered systemic (i.e., administered for 1 week or more) or depot corticosteroids and other immunosuppressive drugs should be used with caution.

Interactions with IMM-101 may be expected with potent steroidal or anti-inflammatory drugs. These drugs should be used with caution as they may attenuate the immune response. The use of these products should be at the discretion of the Investigator who should assess, on a case by case basis, if withholding treatment with these medications is in the patient’s best interest.

Herbal remedies, including traditional Chinese herbal products (e.g., mistletoe) might be expected to have a negative effect on the potential efficacy of IMM-101 and therefore it is recommended that these are not taken during treatment with IMM-101.

Consideration should be given to not co-administering IMM-101 with prophylactic vaccines (e.g., Yellow Fever vaccine or any other live attenuated vaccine).

7.7 ASSESSMENT OF COMPLIANCE

Intra-dermal injections will be administered by the Investigator (or designee) and therefore there will be no need to monitor patient compliance.

Details of each study drug administration (including date and time of the injection, dose and site of administration) will be recorded in the patient's CRF.

8. ASSESSMENT OF EFFICACY

8.1 EFFICACY PARAMETERS

The efficacy objective is to document the long term clinical course of the patients previously enrolled in Study IMM-101-001 in terms of

- Overall survival (OS)
- Reduction in metastatic disease

Overall Survival (OS)

OS is defined as the time from enrolment to death due to any cause. OS will be expressed from time of initial diagnosis, time of enrolment in the Phase 1 study as well as from time of enrolment in this long term follow up study.

Patients without a death date will be censored at the date the patient was last known to be alive.

Reduction in Metastatic Disease

The Investigator will be asked to assess the presence of metastatic disease (if applicable) periodically following CT or MRI scan performed as routine stand of care and record one of the following relative to the previous assessment:

- Worse.
- No change.
- Improved.
- No longer detectable.

8.1.1 Exploratory

Blood samples will be collected and sera prepared for analysis of immunological markers and mediators. Exploratory endpoints may include a change in one or more markers of immune status based on cellular involvement, function or cytokine/immune mediator production such as, for example, cytokines and antibodies, or any other clinically or immunologically relevant assays that may become pertinent during the course of the clinical trial.

Note: Exploratory endpoints will be specified in a separate laboratory manual and will be reported separately to the main safety, tolerability and efficacy endpoints of the study.

8.2 ASSESSING, RECORDING AND ANALYSING EFFICACY PARAMETERS

There are no protocol specified methods to evaluate efficacy parameters and evaluation will be based on the results of the patient's standard care. The methodology used to determine disease stage and tumour size may include chest, abdomen and pelvis CT scans, brain CT scan, and/or bone scans. It is understood that alternative imaging methodologies such as magnetic resonance imaging (MRI) or fluorodeoxyglucose positron emission tomography (FDG-PET) may be used in specific circumstances as part of normal patient care.

9. ASSESSMENT OF SAFETY AND TOLERABILITY

9.1 SAFETY AND TOLERABILITY PARAMETERS

The primary objective for this study is the evaluation of safety and tolerability based on:

- Local and systemic toxicities.
- Adverse Events with documentation of number, type and degree of toxicities as measured by the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 where appropriate

9.1.1 Adverse Events

9.1.1.1 Adverse Event Definition

An adverse event (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.

9.1.1.2 Adverse Drug Reaction

During early development studies clinical experience with a new investigational product or its new usages, particularly as the therapeutic dose(s) may not be established: 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.

Regarding marketed investigational products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

9.1.1.3 Relationship of Adverse Events

Assessment of causality of AEs to the study drug (IMM-101)

Not related: An AE for which there is no reasonable temporal association between its onset and administration of the study drug, or that can reasonably be explained by other factors, including underlying disease, complications, concomitant drugs or concurrent treatment.

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

Unlikely to be related: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possibly related: An AE for which there is a reasonable temporal association between its onset and administration of the study drug (including the course of treatment after withdrawal of the study drug) for which other causal factors may not be excluded.

Probably related: An AE for which there is a reasonable temporal association between its onset and administration of the study drug, including the course after withdrawal of the study drug, and which is more likely to be explained by the study drug than by any other cause (e.g. underlying disease, complications, concomitant drugs or concurrent treatment).

Definitely related: An AE that is judged as undeniably related to administration of the study drug. Factors taken into consideration when a definite relationship is assigned include whether the AE:

- Followed a clear temporal sequence from administration of the study drug.
- Could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- Disappeared or decreased on cessation or reduction in dose of the study drug.
- Reappeared or worsened when the study drug was re-administered.
- Followed a response pattern known to be associated with administration of the study drug.

9.1.1.4 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 v4.0 [5] 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.

9.1.1.5 Treatment-Emergent Adverse Events

All patients will have received IMM-101 in the context of both the Phase 1 study and on a Named Patient basis; therefore all AEs in this long term follow up study will be regarded as treatment-emergent.

9.1.1.6 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., IB for an unapproved investigational product or summary of product characteristics [SmPC] for an authorised product).

The term "expected" in pharmacovigilance is 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.

9.1.1.7 Serious Adverse Events

A serious adverse event (SAE) is one that suggests a significant hazard, contraindication, side-effect, or precaution. With respect to human clinical experience, this includes any event that:

- Results in death (*other than due to disease progression*).
- 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.

* 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.

9.1.1.8 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 Investigator's Brochure [1]) and serious.

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 Investigator's Brochure (1).

All SAEs, whether or not deemed drug-related or expected, must be reported to the relevant pharmacovigilance contact within 24 hours of knowledge by fax in the format detailed by the SAE Reporting Form (see Section 0).

Note: Hospitalisation/death due to disease progression will not be captured as an SAE if the disease progression/death is, in the Investigator's opinion, expected as normal course of the disease. However if the disease progression was faster than expected then a SAE will be reported.

9.1.1.9 Significant Adverse Events

Other significant AEs are defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction or significant additional concomitant therapy.

9.1.2 Laboratory Evaluation

No protocol specific laboratory evaluations will be required other than a urine pregnancy test at screening and at any time during the study if pregnancy is suspected. However, should an abnormal result constituting an adverse event be recorded as part of the patient's standard care, the adverse event shall be recorded in the CRF.

Cell functions, including cytokine production by specific cell population and/or immune activity, and other aspects of the immune response will be analysed as an exploratory endpoint (see Section 8.1.1).

9.1.3 Other Parameters Specific to Study Design

9.1.3.1 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 general and written advice regarding the management of local injection site reactions and generalised systemic symptoms (e.g., pyrexia, headache and general malaise). 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, the injection site must be inspected for local reaction(s). In addition, patients will be asked to assess their injection site reaction, and its effect on their daily activities:

"Has the local reaction affected your daily activities?"

- Not at all
- Slightly
- Moderately
- Quite badly
- Intolerably

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.

In the event of an injection site reaction of Grade 3 (severe) as measured by the NCI CTCAE v4.0 and above, at the discretion of the Investigator, patients may be administered a half dose of the study drug (i.e., a single 0.05 mL intradermal injection of IMM-101) or the time interval between injections of IMM-101 may be extended. Any change in the dose of study drug administered should be recorded in the patient's CRF.

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 CRF.

9.1.3.2 Pregnancy test

A urine pregnancy test will be conducted for all females of child-bearing potential during screening and at any other time during the study if pregnancy is suspected (Study Flow Chart of Assessments, Appendix 1).

The result must be negative for the patient to enter or continue in the study.

9.1.3.3 Prior/Concomitant Medications

Prior and concomitant medications will be recorded at screening and before the first dose of IMM-101. Prior medications will include all medications taken in the 2 weeks before screening. Patients will be asked if they have taken any concomitant medication at each subsequent visit.

Any changes in concomitant medication since the previous visit will also be recorded on the patient's CRF.

9.2 ASSESSING, RECORDING AND ANALYSING SAFETY PARAMETERS

Adverse events will be recorded on the patient's CRF from the time of informed consent (i.e., screening). AEs will be followed until 30 days after the end of study/withdrawal. The Investigator may contact the patient by telephone to obtain the information. See Section 0 for further details. Related SAEs will be recorded regardless of time from last dose.

Injection site reactions will be assessed and recorded in the patient's CRF before each injection of study drug. These will only be recorded as an AE if deemed appropriate by the Investigator. In addition, the patient's assessment of the effect of the injection site reaction on their daily activities will be recorded at each visit, as described in Section9.1.3.1.

9.3 APPROPRIATENESS OF MEASUREMENTS

The maximum volume of blood collected per patient at a single visit (at approximately six-monthly intervals) specifically for the exploratory endpoints will not exceed 6.0 mL.

9.4 RECORDING AND REPORTING ADVERSE EVENT/INTERCURRENT ILLNESSES

It is the responsibility of the Investigator to document all AEs that occur during the study from patient entry. 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 subsequent AEs 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?" Adverse events should be reported on the appropriate page of the CRF.

Each AE will be assigned a CTCAE severity/intensity category as described in Section 9.1.1.4. Further details can be found at the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

If there is a change in severity of an AE, it must be recorded as a separate event.

Every effort should be made by the Investigator to explain each AE and assess its relationship, if any, to study drug treatment. Causality should be assessed using the categories as described in Section 9.1.1.3.

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

In the event of a SAE/SUSAR, the Investigator will notify Emas within 24 hours:

SAE CONTACT DETAILS:

Emas Ltd.
71 Knowl Piece,
Wilbury Way, Hitchin
Hertfordshire, SG4 0TY
Tel.: +44 (0) 1462 422717
Fax: +44 (0) 1462 600456
Email: Drug.Safety@emas-medical.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.

Pregnancy Reporting

Pregnancy, by definition, 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 Emas Drug Safety within 24 hours of the Site Staff becoming aware of the Pregnancy. A Pregnancy Reporting Form must be completed and faxed to Emas Drug Safety.

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 Emas Drug Safety by the submission of a completed SAE form.

9.5 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 30 days after the end of study/withdrawal. The Investigator may contact the patient by telephone to obtain the information.

10. STATISTICS

10.1 STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a brief description (including templates for Tables, Listings, and Figures) of the planned presentation of the results.

All patient data will be presented in separate data listings and summary statistics presented as appropriate.

10.1.1.1 Safety and Tolerability Endpoints

The safety and tolerability endpoints will be summarised using the Safety population.

Local and Systemic Toxicities

Local and systemic toxicities will be presented over the treatment period in standard frequency tables overall and by number, degree and type.

Adverse Events

Summary statistics will be presented descriptively for the following safety endpoints:

- Adverse Events - the number of AEs, the proportion of patients having at least one AE and AEs by coded terms will be presented.
- Related Adverse Events - the number of related AEs, the proportion of patients having at least one related AE and related AEs by coded terms will be presented. Related AEs are defined as events that are definitely, probably or possibly related to study drug or with an unknown relationship.
- Serious Adverse Events - the number of SAEs, the proportion of patients having at least one SAE and SAEs by coded terms will be presented.
- Adverse Events leading to withdrawal or death - the number of AEs, the proportion of patients having at least one AE and AEs by coded terms will be presented.

All AEs will be included in the patient listings and in the above summaries.

10.1.1.2 Other Safety Endpoints

Injection Site Reactions

The frequency and severity of injection site reactions will be summarised.

Other Safety Parameters

All other safety parameters will be summarised using descriptive statistics.

10.1.1.3 Efficacy endpoints

Efficacy endpoints will be analysed using the Safety population.

Disease Status and Progression

Overall survival will be summarised by Kaplan-Meier curves. Median survival estimate as well as associated 95% CI will be reported.

Reduction in Metastatic Disease

The changes in metastatic disease will be presented over the treatment period in standard data listings by time-point.

10.1.1.4 Exploratory Endpoints

Variables for the exploratory endpoints will be analysed and reported separately to the main efficacy and safety endpoints of the study.

10.1.2 Interim Analysis

No formal interim analysis is planned for this study although data will be presented on a periodic basis for the annual Development Safety Update Report. Further analysis will be conducted as required.

10.2 SAMPLE SIZE

N/A

10.3 LEVEL OF SIGNIFICANCE

N/A

10.4 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 6.4.

10.5 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED AND SPURIOUS DATA

Missing, unused and spurious data will be treated as such.

10.6 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.

10.7 PATIENT SELECTION FOR ANALYSES

10.7.1 Analysis Sets

The definition of the analysis set is in line with the ICH E9 guidelines.

Just one analysis set will be defined:

- Safety analysis set: All patients who receive at least one dose of the study drug.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical monitor(s) should be given direct access to primary patient data (i.e., source data) which supports the data on the CRFs 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.

Other authorised persons such as auditors may need to have direct access to this source data.

11.1 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).

11.2 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).

11.3 DIRECT ACCESS

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g., domestic and foreign regulatory authorities, Sponsor or 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.

12. 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 Contract Research Organisation (CRO), the QA department of the Sponsor, or a regulatory authority.

12.1 QUALITY CONTROL

Quality Control is defined as the operational techniques and activities undertaken within the quality assurance 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.

12.2 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.

12.2.1 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.

12.2.2 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.

13. ETHICS

13.1 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 World Medical Association Declaration of Helsinki, as amended, 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 the United Kingdom.

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.

13.2 INDEPENDENT ETHICS COMMITTEE APPROVAL

Before initiating a study, the Investigator should have written and dated approval/favourable opinion from the relevant IEC for the study Protocol (and any amendments), written ICF, consent form updates, 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 should provide to the IEC all documents that are subject to review.

The Sponsor will ensure an Investigator's Brochure is available and will supply the Investigator with the Investigator's Brochure and Protocol for the Investigator to submit to the local IEC for the Protocol's 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.

The IEC must be informed by the Investigator of all subsequent Protocol amendments and of unexpected SAEs occurring during the study, which are likely to affect the safety of the patients or the conduct of the study. Approval for such changes must be transmitted in writing to the Sponsor by the Investigator.

The Investigator should provide the IEC with all relevant amendments or updates of the Protocol and Investigator's Brochure. Also, the Investigator should provide written reports to the IEC annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted by the Investigator to the IEC.

13.3 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 and signed by the patient and the Investigator obtaining the consent. The informed consent form 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.

In the case of withdrawal, separate consent will be sought to allow the continued collection on patient status.

13.4 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 IEC of an amendment. The only exceptions are where 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 the MHRA.

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 the Investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1 COMPLETION OF CASE REPORT FORMS

All CRF entries must be made in black ink for duplication purposes. The Investigator must ensure the accuracy, completeness legibility and timeliness of data reported in the CRF and all required reports. Any change or correction to a CRF must be dated, initialled and explained (if necessary) and must not obscure the original entry.

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

14.2 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.

15. 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.

16. 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.

17. ADMINISTRATIVE PROCEDURES

17.1 STUDY PERSONNEL

Before the start of the study, each Investigator must supply the Sponsor or its designated CRO 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).

17.2 STUDY MONITORING

The Sponsor or its designated CRO are responsible for ensuring the proper conduct of the study with regards to Protocol adherence and validity of the data recorded on the CRF. 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 Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data entered on the CRFs and in all required reports. Data entered on the CRF, which are derived from source documents, should be consistent with the source documents (or the discrepancies should be explained).

17.2.1 Return of Case Report Forms

Before acceptance, the clinical monitor will review the CRFs for completeness and adherence to the Protocol.

17.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Before shipment of investigational product, the following documents must be submitted/returned to the Sponsor or its designated CRO by the Investigator:

- Signed final version of the Protocol.
- Signed, initialled and dated (within the last 12 months) *curriculum vitae* of the Investigator(s) *(and other relevant staff, if required)*.
- Copy of the letter or notice from the IEC approving the final version of this Protocol and Patient Information Sheet and ICF.
- Signed Investigator Financial Agreement.

The following documents must also be available:

- Approved Patient Information Sheet/ICF Approval Form.
- Sample Drug dispensing record.
- Written national regulatory approval.
- Written insurance statement (e.g., Association of the British Pharmaceutical Industry [ABPI] indemnity).

18. REFERENCES

1. Investigator's Brochure, IMM-101: A Suspension of Whole Cell Heat-Killed Mycobacterium obuense in Borate-Buffered Saline for Intradermal Injection. Version 4, 10 Jan 2011.
2. Dunn GP, Old LJ, Schreiber RD (2004b). The three Es of cancer immunoediting. *Annu Rev Immunol* 22:329-360
3. Gulley JL, Arlen PM, Bastian A, et al. Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. Clin Cancer Res. 2005; 11: 3353-62.
4. Arlen PM, Gulley JL, Parker C et al. A randomized phase II study of concurrent docetaxel plus vaccine versus vaccine alone in metastatic androgen-independent prostate cancer. Clin Res Cancer. 2006; 12: 1260-9.
5. Cancer Therapy Evaluation Program, Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0, DCTD, NHI, DHHS, 28 May 2009.
6. Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649-655.

19. APPENDICES

Appendix 1 Study Flow Chart of Assessments

Appendix 2 WHO Performance Status

Appendix 3 Study Acknowledgement / Protocol Signature Page

Appendix 4 Summary of Protocol Amendments

Appendix 1

Study Flow Chart of Assessments

	Screening Phase	Treatment Phase								
Day / Week	Day -28 to 0	Week[5]								
		Day 0	4, 8, 12, 16, 20	24	28, 32, 36, 40, 44	48	52, 56, 60, 64, 68	72	76, 80, 84, 88, 92	96[3]
Visit window (± days)[1]	-	-	14	14	14	14	14	14	14	14
Informed Consent	✓									
Inclusion/Exclusion Criteria	✓	✓[2]								
Demography & Baseline Data	✓									
Complete Medical History	✓									
Disease Staging	✓									
Blood Samples for Exploratory Endpoints[7]		✓		✓		✓		✓		✓
Urine Pregnancy Test[4]	✓									
IMM-101 Administration		✓	✓	✓	✓	✓	✓	✓	✓	✓
Check time interval since last dose of IMM-101 is ≥14 days		✓	✓	✓	✓	✓	✓	✓	✓	✓
Assess Injection Site Reactions [7]	✓[6]	✓[6]	✓	✓	✓	✓	✓	✓	✓	✓
Prior/Concomitant Therapy[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Reporting[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

1. The dose given and/or the interval may be modified at the discretion of the Investigator provided the minimum period between doses is no less than 14 days.
2. Inclusion/exclusion criteria will be re-checked before commencing any study treatment.
3. Should the study continue beyond 96 weeks, the same pattern of assessments will continue for subsequent visits as described in this flow chart.
4. Urine pregnancy tests should be repeated as warranted during the study.
5. Nominal week numbers are stated.
6. Check for pre-existing injection site reactions.
7. If the dosing interval is increased, the patient should still attend the study site for safety assessments preferably every 3 months but, if this is not possible, every 6 months at a minimum. The blood sample for exploratory analysis should continue to be taken every 6 months. In addition, if the patient does not attend the clinic for a study visit within a calendar month, the clinic will telephone the patient to enquire about injection site reactions, adverse events, concomitant medications and any other concerns.

Appendix 2

WHO PERFORMANCE STATUS

WHO performance status assessment:

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

Oken *et al* (1982) [6]

Appendix 3

STUDY ACKNOWLEDGEMENT / PROTOCOL SIGNATURE PAGE

Investigator's Statement:

I have read and understand the foregoing Protocol entitled "**An Open Label Long-term Follow-up Study for Melanoma Patients who were Previously Enrolled in the Phase I Study IMM-101-001**", study number **IMM-101-008, EudraCT No. 2011-003967-31** and agree to conduct the Study, in compliance with Good Clinical Practice (CPMP/ICH/135/95), 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.

Angus Dalgleish	Prof of oncology.
Investigator's Name (please print)	Investigator's Title
8 Jun 2015	
Date (dd-mmm-yyyy)	Investigator's Signature

APPENDIX 4

SUMMARY OF PROTOCOL AMENDMENTS

PROTOCOL AMENDMENT 1.0

This Protocol amendment, dated 21st November 2011, addressed the following change to the study Protocol (Final Version 1.0, dated 15th September 2011):

1. To reduce the volume of blood taken at six monthly intervals for the analysis of exploratory immunological endpoints.

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 2.0

This Protocol amendment, dated 13 February 2012, addressed the following changes to the study Protocol (Final Version 2.0, dated 21st November 2011):

1. A change in the third party contract responsible for SUSAR reporting. The responsibility for SUSAR reporting was transferred from Theradex (Europe) Limited to Emas Ltd., Hitchin, Herts., UK

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 3.0

This Protocol amendment, dated 25th June 2012 addressed the following changes to the study Protocol (Final Version 3.0, dated 13th February 2012):

- Change in the identity and site of the drug substance manufacturer.
- Change in Vial Size
- Revised Fax Number for the Pharmacovigilance Service Provider

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 4.0

This protocol amendment, dated 1st November 2013 addressed the following changes to the study Protocol (Final Version 4.0, dated 1st July 2012):

- Inclusion of collection of information on subject status following withdrawal from the study subject to provision of informed consent

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 5.0

This protocol amendment, dated 28th July 2014 addressed the following changes to the study Protocol (Final Version 5.0, dated 1st November 2013):

- Clarification of need for study safety assessments (assessment of injection site reactions, recording of adverse events and concomitant medications) to be taken preferably every 3 months but, if not possible due to patient availability, every 6 months at a minimum.
- Clarification of reason for decreasing dose of study medication or increasing dosing interval due to previous injection site reactions.
- Change of Medical Director from Robert Tansley to Frances MacIntosh

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 6.0

This protocol amendment, dated 7 November 2014 addressed the following changes to the study Protocol (Final Version 6.0, dated 28th July 2014):

- Inclusion of the requirement that, if the patient does not attend the clinic for a study visit within a calendar month, the clinic will telephone the patient to enquire about injection site reactions, adverse events, concomitant medications and any other concerns the patient may have. Details of the call will be recorded in the patient notes with appropriate information on adverse events and concomitant medications also being recorded in the CRF. The maximum volume of blood collected per patient at a single visit (at approximately six-monthly intervals) specifically for the exploratory endpoints has been changed from 'will not exceed 5.0 mL' to 'will not exceed 6.0 mL' as the correct vacutainer is available in a 6 mL size.

This Protocol Amendment was considered **non-substantial**.

PROTOCOL AMENDMENT 7.0

This protocol amendment, dated 05 June 2015 addressed the following changes to the study Protocol (Final Version 7.0, dated 7 November 2014):

- To show the inclusion of St George's Hospital as an additional site.
- To show the change of address of Immodulon Therapeutics.
- Update the IMP out of fridge storage recommendation from 'The product must be used within 2 hours of being removed from the fridge' to 'The product must be used with 6 hours from being removed from the fridge.
- Addition of the out of hours telephone number.
- To remove progression-free survival from the study endpoints, due to no protocol-specified assessment schedule for CT scans.
- To amend the presentation of the reduction in metastatic disease data to data listings only, due to CT scans not being a protocol-specified requirement, and change is recorded relative to previous assessment.