Clinical Study Protocol IMCgp100-401

An Open-label, Multi-Center, Rollover Study in Patients with Advanced Melanoma After Completing an IMCgp100 Clinical Study

Sponsor: Immunocore, Ltd.

EUDRACT Number: 2016-002236-32

Protocol Version: 3.0

Release Date: 07 November 2016

Sponsor Emergency Contact:

[redacted]

This study will be conducted in compliance with the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

AMENDMENT 2

Amendment Rationale

The pattern of clinical response to immunotherapeutic agents differs from that observed with cytotoxic therapies. There is accumulating evidence that a proportion of patients with advanced melanoma treated with immunotherapy agents, including IMCgp100, may develop initial radiographic progression of the tumor before demonstrating meaningful clinical benefit. This delayed response to therapy or immune-mediated tumor flare have been coined as "pseudo-progression" that can then be followed by prolonged periods of disease stabilization or objective tumor responses. To allow for patients to continue therapy beyond an initial assessment of progressive disease according to RECIST v1.1, this amendment provides additional detail delineating criteria for treatment beyond progression. Patients must meet specific clinical criteria and provide additional informed consent to continue therapy beyond an initial assessment of disease progression.

Changes to the Protocol

1. Added criteria for treatment beyond progression (Section 6.6.1) and rationale (Section 2.4) and treatment discontinuation in the setting of treatment beyond progression
2. Clarified that the dose and regimen of IMCgp100 will be determined based upon the dose and schedule utilized in the parent study
3. Extended the safety follow-up period from 30 days to 90 days
4. Minor edits to clarify language, improve content flow and readability

Institutional Review Board/Independent Ethics Committee

A copy of this amended protocol will be sent to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Health Authorities. The changes described in this amended protocol require IRB or IEC approval. Changes herein affect the Informed Consent, and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol. The revised informed consent form will replace the previous informed consent form.

AMENDMENT 1

Amendment Rationale

Amendment 1 for this protocol serves to clarify the required hospitalizations for treatment with IMCgp100.

Changes to the Protocol

1. Hospitalization requirements are clarified
2. Minor editss to clarify language, improve content flow and readability

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PROTOCOL SIGNATURES

Sponsor Signature

I have read the protocol and confirm that the protocol follows the current Good Clinical Practice guidelines.

Approved By:

Principal Investigator Signature

I, the undersigned, have reviewed the amended protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the tripartite International Conference on Harmonization guideline E6 (R1): Guideline for Clinical Practice and all the ethical and regulatory considerations stated.

I have read and understood the contents of the Investigator's Brochure for IMCgp100.

[redacted]

[redacted]

[redacted]

[redacted]
Institution Name

PROTOCOL SYNOPSIS

Study Number	IMCgp100-401
Title	An Open-label, Multi-center, Rollover Study in Patients with Advanced Melanoma After Completing an IMCgp100 Clinical Study
Brief Title	IMCgp100-401 Rollover Study
Sponsor	Immunocore, Ltd.
Investigational Agents	IMCgp100 administered on a weekly (QW) basis.
Study Type	Interventional
Study Purpose and Rationale	IMCgp100-401 is a rollover study that is designed to provide continued access to IMCgp100 for eligible patients with advanced melanoma who have previously participated in an IMCgp100 study (parent study). Parent studies that are eligible for patients to continue to receive IMCgp100 in this rollover study must have completed and satisfied its primary endpoints or have been terminated by the Sponsor for reasons other than safety. Eligible patients will have tolerated IMCgp100 for a minimum of 4 weeks of dosing without significant toxicities that would preclude further dosing in the opinion of the principal investigator or Sponsor and have no evidence of unequivocal progressive disease. The rollover study will provide continued access to IMCgp100 for all patients treated on a completed IMCgp100 clinical study for whom there is evidence of continued benefit from treatment with IMCgp100 and for whom alternative therapies are not available. Patients will enroll in the IMCgp100 rollover study and the principal investigator and Sponsor will determine the regimen and dose for patients to receive in the rollover using guidance from the previous (parent study).
Primary Objective	The primary objective is to determine the number of patients with adverse events (AEs) associated with IMCgp100 treatment.

Secondary Objectives	• To characterize the long-term safety (> 1 year dosing) and tolerability profile associated with treatment with IMCgp100 • To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100 • To estimate the overall survival (OS) in patients treated with IMCgp100
Study Design	This rollover study will enroll patients who are currently receiving IMCgp100 treatment and for whom the parent IMCgp100 clinical study completes. At the time of parent study completion, the rollover study will enroll all patients actively receiving IMCgp100 treatment in the parent study in order to continue to provide patient access to treatment. Patients who enroll in the rollover study will, in the opinion of the investigator, continue to receive clinical benefit from treatment with IMCgp100. Patients who are receiving treatment as part of an ongoing and not yet completed study, are not eligible to participate in the rollover study until the time of study completion. At the time of rollover study entry, patients can continue to receive the current dose from the parent study or an alternative dose can be implemented with written agreement from the Sponsor. Doses higher than that in the parent in study will not be permitted. • For patients from the IMCgp100-01 parent study the maximum dose will be the recommended Phase II dose (50 mcg flat dose) All patients must sign the rollover study consent form and be enrolled in the new study. All assessments will commence with Rollover Cycle 1. Safety assessments (physical examinations, clinical laboratory, electrocardiogram (ECG) assessments, and continuous monitoring of AEs) will continue throughout the study at the described intervals. Patients will continue to receive IMCgp100 until loss of clinical benefit for the individual patient (as per local imaging with a minimum interval of 12 weeks and the protocol-specified response criteria), unacceptable toxicity as defined by the principal investigator or Sponsor, withdrawal of consent, loss to follow up, or death. No efficacy or biomarker endpoints will be collected as part of the rollover study. Date of death will be collected to assess overall survival (OS) only. Imaging of disease will continue as described in the study

	protocol using modified immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).
Population Under Study	The rollover study will enroll patients who have been treated as part of an IMCgp100 clinical study that has completed. At the time of rollover study entry, patients must be continuing to receive IMCgp100 as part of the active parent study and for whom the study is completing. Patients must not have any ongoing, serious IMCgp100-related toxicities at the time of rollover study entry that would preclude further dosing in the opinion of the investigator or the Sponsor.
Inclusion Criteria	1. Patient is currently participating in an Immunocore-sponsored study of IMCgp100 and is actively receiving IMCgp100. Patient must have fulfilled all required assessments in the parent study (unless the study is being terminated) 2. Patient is currently receiving clinical benefit from the treatment with IMCgp100, as determined by the principal investigator from the parent study 3. Patient has demonstrated compliance with the parent study requirements, as assessed by the principal investigator and patient is able to comply with the necessary visits and assessments as part of the rollover study 4. Written informed consent must be obtained prior to enrolling in the roll-over study and receiving study treatment. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness
Exclusion Criteria	1. Patient has been permanently discontinued from any IMCgp100 study or from IMCgp100 treatment in the parent study due to unequivocal progressive disease, unacceptable toxicity, non-compliance to study procedures, withdrawal of consent, or any other reason 2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test 3. Women of child-bearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using 2 methods of

	highly effective contraception from Screening, and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods include barrier methods, intrauterine devices, or hormonal methods. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Women of child-bearing potential must have a negative serum pregnancy test at Screening. Otherwise, female patients must be post-menopausal (no menstrual period for at least 12 months prior to Screening), or surgically sterile 4. Male patients who are not surgically sterile unless they are using a double barrier contraception method from enrollment through treatment and for 6 months following administration of the last dose of study drug
Efficacy Assessments	No efficacy assessments will be collected in this rollover study. Patients will be assessed for tumor progression using protocol-specified modified irRECIST criteria at a minimum of every 12 weeks.
Safety Assessments	Safety will be monitored by assessing physical examination, vital signs, body height and weight, hematology, chemistry, pregnancy, ECG, cytokine testing, as well as collecting of the AEs at every visit.
Keywords	IMCgp100, melanoma, gp100, rollover

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
AESI	Adverse event of special interest
Anti-CD3	Anti-cluster of differentiation 3
C#D#	Cycle # day #
CD3	Cluster of differentiation 3
C_{max}	Maximum observed concentration
CRO	Contract research organization
CTL	Cytotoxic T lymphocyte
DLT	Dose limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FAS	Full analysis set
GCP	Good clinical practice
HLA-A2	Human leukocyte antigen-A2
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMCgp100	77 kDa bi-specific protein
IRB	Institutional Review Board
irRECIST	Immune-related response evaluation criteria in solid tumors
IV	Intravenous
kD	Binding affinity
MTD	Maximum tolerated dose
nM	Nanomolar
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
NSAID	Non-steroidal anti-inflammatory drug.
OS	Overall survival
PD	Progressive disease
PK	Pharmacokinetics
pM	Picomolar
QD	Every day
QW	Every week
RC#	Rollover cycle #

REB	Research ethics board
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II dose
RP2D-QD	Recommended Phase II dose – daily
RP2D-QW	Recommended Phase II dose — weekly
SAE	Serious adverse event
SUSAR	Suspected, unexpected, serious adverse reaction
$t_{½}$	Distribution and elimination half-life
$T_{½}$	Terminal binding half-life
UM	Uveal melanoma

1 BACKGROUND

1.1 Overview of Disease Setting

Melanoma arises from pigment containing cells (melanocytes) present in the skin, eye, and mucus membranes. Melanoma most frequently occurs in the skin; however, ocular melanoma arises from pigmented cells in the eye. The primary cause of melanoma is thought to be radiation-induced deoxyribonucleic acid damage from ultraviolet light exposure. Melanoma is the most deadly of skin cancers. Globally, in 2012, melanoma occurred in 232,000 people and resulted in 55,000 deaths. It is estimated that almost 76,000 new diagnoses of melanoma will be made in 2016 in the United States, and approximately 10,000 people are expected to die of melanoma (American Cancer Society, 2016). In addition, the rate of diagnosis of melanoma continues to rise at a significant rate; according to 2013 Surveillance, Epidemiology, and End Results data, the average incidence rate rose 1.4% each year for the last decade, and melanoma is now the sixth most common cancer diagnosis in the United States (Surveillance, Epidemiology, and End Results, 2015). Cutaneous and uveal melanoma (UM) is more common in men than women. UM is a rare type of melanoma where the incidence has ranged from 5.3 to 10.9 cases per million (Singh, 2003).

1.2 Overview of IMCgp100

IMCgp100 is a 77 kDa bi-specific protein with targeting and effector moieties which is manufactured in *Escherichia coli*, *E coli*. The targeting portion of IMCgp100 (the T cell receptor) functions to bind to the gp100 antigen as presented by major histocompatibility complex Class I on the surface of melanoma cells. The targeted gp100 peptide is presented by a subset of the population that express a specific variant of the major histocompatibility complex Class I complex known as human leukocyte antigen-A2 (HLA-A2). This variant is carried by approximately 50% of the population in the Western World (Middleton, 2003).

The effector function (anti-cluster of differentiation 3 [anti-CD3]) works by binding and activating T cells via cluster of differentiation 3 (CD3). These T cells can be tumor-specific cells which are already resident in the tumor (tumor infiltrating lymphocytes), [redacted]

1.3 Non-clinical Experience with IMCgp100

1.3.1 Pre-clinical Pharmacology Summary

IMCgp100 has been shown to induce the full repertoire of cytotoxic T lymphocyte (CTL) activation events in a dose-dependent manner in vitro when combined with target melanoma cells. [redacted] he activation of CD4 T cells has also been demonstrated at similar concentrations and with similar kinetics. Such activation would be expected to augment the CTL-mediated immune response through the recruitment of other inflammatory cells.

Using peripheral blood mononuclear cells from melanoma patients, IMCgp100 has been shown to augment an already present anti-tumoral response. Finally, the tumor infiltrating T cells that would be the first line of attack in a clinical situation would be expected to be outnumbered by melanoma targets; therefore, a single T cell is capable of serial killing in vitro.

These data demonstrate that IMCgp100 is a potent tumor-killing agent.

1.3.2 Non-clinical Toxicology Summary

Both the gp100-specific soluble T cell receptor and the CD3 targeting ends of IMCgp100 have been demonstrated to have high specificity for the human HLA-A2-gp100 peptide complex and human CD3. Therefore, binding and activation of IMCgp100 cannot be demonstrated in non-human primates, which show a relatively high degree of sequence homology to human CD3. In addition, both the T cell receptor targeting end and CD3 activation arm do not interact at any level in any other species. Given the limitations in binding of IMCgp100 and activation of any T cell subsets in any standard toxicology species, there is no relevant toxicology species in which IMCgp100 can be tested.

Tissue cross-reactivity studies with IMCgp100 and published gp100 immunohistochemistry demonstrate gp100 expression in human melanocytes, and expression levels have been demonstrated directly in the retina, melanocytes, the substantia nigra, and the thymus (Takase, 2005; Wagner, 1997). [redacted]

[redacted]

[redacted]

1.4 Clinical Program and Safety Summary

IMCgp100 is being studied in an ongoing first-in-human, open-label, dose escalation study (IMCgp100-01). Patients with advanced melanoma were enrolled into 2 separate dose escalation cohorts: (1) a weekly (QW) dosing regimen cohort, and (2) a daily (QD) dose x 4 days repeated every 3 weeks dosing regimen cohort. The study was designed to identify the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of IMCgp100 in the 2 repeat dosing regimens: (1) weekly dosing (the RP2D-QW) and (2) daily dosing x 4 days (the RP2D-QD).

1.4.1 Weekly Dosing: Dose Escalation Results

The weekly dosing regimen dose escalation included dose levels from 5 ng/kg up to 900 ng/kg, and the MTD for this dosing regimen was identified at 600 ng/kg QW (Middleton, 2015). In the review of the safety and pharmacokinetic (PK) data for the weekly dosing regimen, the RP2D-QW was initially identified as a flat dose of 50 mcg administered intravenously (IV) on a weekly basis; [redacted]

[redacted]

[redacted]

[redacted]

Cytokine analyses of the peripheral circulation combined with clinical findings in patients treated with weekly dosing revealed rare cases of severe, systemic cytokine release syndrome. As a consequence of on-target skin or tumor activity, with consequential cytokines permeating into the periphery, many patients showed modest, drug-induced levels of 1 or more inflammatory cytokines [redacted]

Please refer to the current IMCgp100 Investigator's Brochure for details.

1.4.2 Weekly Dosing: Recommended Phase II Dosing of the Weekly Regimen (RP2D-QW) Cohort Results

A review of the PK and safety data from the QW dose escalation cohorts suggested that the more severe toxicities and higher drug exposures of IMCgp100 were associated with the higher absolute doses administered. Based on these data and the range of absolute doses administered at the MTD of 600 ng/kg (n=5 pts, range 34–66 mcg QW, median dose of 54 mcg), the RP2D-QW was initially determined to be a flat dose of 50 mcg administered on a weekly basis. [redacted]

[redacted]

1.4.3 Daily Dosing: Dose Escalation Results

The dose escalation in the daily dosing regimen Phase I arm (Arm 2) is complete with the dosing regimen identified as a flat dose of 50 mcg QDx4 administered every 3 weeks (n=15 patients across 5 dose levels ranging from 10 mcg to 50 mcg). [redacted]

For further details refer to the most recent version of the IMCgp100 Investigator's Brochure.

1.4.4 Preliminary Pharmacokinetic Data from First-in-human IMCgp100-01 Study

[redacted]

[redacted]

For detailed information regarding PK data of IMCgp100, refer to the IMCgp100 Investigator's Brochure.

2 RATIONALE

2.1 Study Rationale and Purpose

IMCgp100-401 is a rollover study that is designed to provide continued access to IMCgp100 for eligible patients with advanced melanoma who have previously participated in an IMCgp100 study (parent study). Parent studies that are eligible for patients to continue to receive IMCgp100 in this rollover study must have completed and satisfied its primary endpoints or have been terminated by the Sponsor for reasons other than safety.

Eligible patients for the rollover study will have tolerated IMCgp100 for a minimum of 4 weeks of dosing without significant toxicities that would preclude further dosing in the opinion of the principal investigator or of the Sponsor and have no evidence of unequivocal progressive disease (PD).

2.2 Rationale for Study Design

The rollover study will provide continued access to IMCgp100 for all patients treated on a completed IMCgp100 clinical study for whom there is evidence of continued benefit from treatment with IMCgp100 and for whom alternative therapies are not available. Patients will enroll in the IMCgp100 rollover study and the principal investigator and Sponsor will determine the regimen and dose for patients to receive in the rollover using guidance from the previous (parent study).

Please see Section 2.3 below for dose and regimen details.

2.3 Rationale for Treatment Dose and Regimen

Patients enrolled in this rollover study will enter this study with a defined dose and regimen from the parent study. Patients can continue to receive the current dose and regimen from the parent study (Table 2-1) or an alternative dose can be implemented with written agreement from the Sponsor. Doses higher than that administered in the parent in study will not be permitted.

- For patients from the IMCgp100-01 parent study the maximum dose will be the RP2D flat dose (50 mcg)

Table 2-1 Maximum Dose and Schedule of Administration Based Upon Parent Study

Study Protocol	Maximum IMCgp100 Dose and Frequency of Administration
IMCgp100-01	50 mcg IV weekly (QW)

2.4 Rationale for Treatment Beyond Initial Progression in Select Settings

There is accumulating evidence in the field of immune-oncology that some patients treated with immune therapy agents, such as IMCgp100, may develop initial progression of the tumor, as evidenced on computed tomography (CT) or magnetic resonance imaging (MRI), before demonstrating meaningful clinical benefit from the treatment with disease stabilization or subsequent objective response after the initial progression is noted (Hodi, 2016). Such cases were noted in the Phase I development of IMCgp100 (Middleton, 2015; Middleton, 2016). In light of these data, patients who demonstrate an initial progression by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 may continue to receive study treatment with IMCgp100 until further progression under the management principles of immune-related response criteria (irRECIST) criteria (where a second, confirmatory scan is required for confirmation of progression) provided that such patients are assessed by the investigator as deriving clinical benefit from, and tolerating treatment with IMCgp100 (Eisenhauer, 2009; Wolchok, 2009). See Section 6.6.1 for details regarding criteria for treatment with IMCgp100 beyond initial progression by RECIST v1.1.

3 STUDY DESIGN

3.1 Description of Study Design and Populations

This is a study of IMCgp100 conducted to provide continued access to IMCgp100 treatment for patients enrolled in a completed clinical study of IMCgp100. Patients enrolled in the rollover study must be currently receiving IMCgp100 within an IMCgp100 clinical study that has completed. Patients must meet all selection criteria defined in this rollover study Section 5. Patients do not need to be re-assessed against the parent study entry criteria at the time of enrollment in the rollover study.

This rollover study will enroll patients who are currently receiving IMCgp100 treatment and for whom the parent IMCgp100 clinical study completes. At the time of parent study completion, the rollover study will enroll all patients actively receiving IMCgp100 treatment in the parent study in order to continue to provide patient access to treatment. Patients who enroll in the rollover study will, in the opinion of the investigator, continue to receive clinical benefit from treatment with IMCgp100. Patients who are receiving treatment as part of an ongoing, and not yet completed, study are not eligible to participate in the rollover study until the time of study completion.

At the time of rollover study entry, patients can continue to receive the current dose from the parent study or an alternative dose can be implemented with written agreement from the Sponsor. Doses higher than that in the parent in study will not be permitted.

- For patients from the IMCgp100-01 parent study the maximum dose will be the RP2D flat dose (50 mcg)

See Table 6-1 in Section 6.1 Study Treatment details in the rollover study. All patients must sign the rollover study consent form and be enrolled in the new study. All assessments will commence with Rollover Cycle 1. Safety assessments (physical examinations, clinical laboratory, and electrocardiogram [ECG] assessments, as well as continuous monitoring of AEs) will continue throughout the study at the described intervals. Patients will continue to receive IMCgp100 until loss of clinical benefit for the individual patient (Section 6.6.1), unacceptable toxicity as defined by the principal investigator or Sponsor, withdrawal of consent, loss to follow-up, or death.

No efficacy or biomarker assessments will be collected as part of the rollover study. Date of death will be collected to assess overall survival (OS) only. Patients will be assessed for tumor progression using protocol-specified modified immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) with a minimum interval of imaging of every 12 weeks.

3.2 Definition of Study Periods

The **Screening Period** will begin once a patient has signed the consent form and concludes with either a screen failure decision or initiation of study dosing on Rollover C1D1 (RC1D1). During the Screening

Period, patients are evaluated against the study inclusion and exclusion criteria (see Section 5 Population Selection Criteria). The screening window for all procedures will be up to 21 days. Please note, if the last dose of IMCgp100 on the parent study and the first dose of IMCgp100 on the rollover study are separated by more than 21 days, the first dose of IMCgp100 must be administered with overnight inpatient monitoring; given the risk of severe infusion-related toxicity and potential for hypotension (refer to Section 1.4 for details of clinical experience with IMCgp100).

The **Treatment Period** will begin with the first treatment in the first cycle with RC1D1. For the purpose of treatment scheduling, a cycle consists of 4 weeks. The Treatment Period consists of the time from RC1D1 until the end of study treatment.

The **90-day Safety Follow-up Period** consists of the time from the last dose of study medication for a period of 90 days. Safety observations during this 90-day Follow-up Period are outlined in Section 7.2.3 and include reporting of all AEs and all serious AEs (SAEs) in the same manner as the Treatment Period.

The **Survival Follow-up Period** will initiate after the 90-day Follow-up Period and continue until death. As applicable, all patients will be followed for survival until the end of the study is reached.

3.3 Definition of End of Treatment

In all patients in this study, IMCgp100 will be administered IV according to the defined regimen. Patients will continue to receive IMCgp100 until loss of clinical benefit for the individual patient (as per local imaging standard of care and the appropriate response criteria, as defined by the principal investigator), unacceptable toxicity as defined by the principal investigator or Sponsor, withdrawal of consent, loss to follow-up, or death.

3.4 Definition of End of Study

The end of the study will be when all patients enrolled have completed IMCgp100 treatment or the study is terminated by the Sponsor.

3.5 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor. Should this be necessary, any ongoing patient should be seen as soon as possible for end of treatment (EOT) visit and the assessments should be performed as described in Table 7-1.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. Under guidance of the Sponsor, the investigator will be responsible for informing the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) of the termination of the trial.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

The primary objective is to determine the number of patients with AEs associated with IMCgp100 treatment.

4.2 Secondary Objectives

- To characterize the long-term safety (> 1 year dosing) and tolerability profile associated with treatment with IMCgp100
- To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100
- To estimate the OS of patients treated with IMCgp100

4.3 Primary Endpoint

The primary endpoint is incidence of AEs associated with IMCgp100.

4.4 Secondary Endpoints

- Tolerability: Dose interruptions, reductions, and dose intensity of IMCgp100
- Assessments of anti-IMCgp100 antibody formation
- Date of death in all patients treated with IMCgp100

Table 4-1 Objectives and Related Endpoints

Objective(s)	Endpoint(s)
Primary	
To determine the number of patients with adverse events associated with IMCgp100 treatment	Incidence of adverse events
Secondary	
To characterize the long-term safety (> 1 year dosing) and tolerability of IMCgp100	Tolerability: Dose interruptions, reductions, and dose intensity of IMCgp100

Table 4-1 Objectives and Related Endpoints

Objective(s)	Endpoint(s)
To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100	Assessments of anti-IMCgp100 antibody formation
To estimate the overall survival in patients treated with IMCgp100	Date of death in all patients treated with IMCgp100

5 POPULATION SELECTION CRITERIA

5.1 Patient Population

This rollover study will enroll patients who have been treated as part of an IMCgp100 clinical study that has completed. At the time of rollover study entry, patients must be continuing to receive IMCgp100 as part of the active parent study and for whom the study is completing. Patients must not have any ongoing, serious IMCgp100-related toxicities at the time of rollover study entry that would preclude further dosing in the opinion of the investigator or the Sponsor.

5.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient is currently participating in an Immunocore-sponsored study of IMCgp100 and is actively receiving IMCgp100. Patient must have fulfilled all required assessments in the parent study (unless the study is being terminated)

2. Patient is currently receiving clinical benefit from the treatment with IMCgp100, as determined by the principal investigator from the parent study

3. Patient has demonstrated compliance with the parent study requirements, as assessed by the principal investigator and patient is able to comply with the necessary visits and assessments as part of the rollover study

4. Written informed consent must be obtained prior to enrolling in the rollover study and receiving the study treatment. If consent cannot be expressed in writing, then the consent must be formally documented and witnessed, ideally via an independent trusted witness

5.3 Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patient has been permanently discontinued from any IMCgp100 study or from IMCgp100 treatment in the parent study due to unequivocal PD, unacceptable toxicity, non-compliance to study procedures, withdrawal of consent, or any other reason

2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test

3. Women of child-bearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using 2 methods of highly effective contraception from Screening, and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Highly effective methods include barrier methods, intrauterine devices or hormonal methods. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Women of child-bearing potential must have a negative serum pregnancy test at Screening. Otherwise, female patients must be post-menopausal (no menstrual period for at least 12 months prior to Screening), or surgically sterile

4. Male patients who are not surgically sterile unless they are using a double barrier contraception method from enrollment through treatment and for 6 months following administration of the last dose of study drug

6 STUDY TREATMENTS AND ADMINISTRATION

6.1 Study Treatment

For this study, the investigational drug refers to IMCgp100. Study drug will be supplied by the Sponsor, Immunocore.

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record electronic case report form (eCRF).

Table 6-1 Dose and Treatment Schedule

Study Treatment	Pharmaceutical Form and Route of Administration	Dose	Frequency and/or Regimen
IMCgp100	[redacted]	[redacted]	Weekly

For all study medication administration, a physician must be present at the site or immediately available to respond to emergencies during all administrations of all study medications. Fully functional resuscitation facilities should be available. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Concomitant Therapy

6.2.1 Permitted Concomitant Therapy

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed in general. Examples include anti-diarrheal medications, anti-emetics, or electrolyte supplementation.

Patients must be told to notify the investigational site staff about any new medications, herbal remedies, or dietary supplements that he or she takes after the start of the study treatment, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications, and blood transfusions) administered during the study must be listed on the Concomitant Medications or other relevant eCRF.

IV hydration required to manage toxicity associated with any of the study treatments (eg, hypotension) should be recorded in the Concomitant Medications eCRF. IV hydration prior to administration of study treatments does not need to be recorded in the eCRF unless fluids are prescribed to manage toxicity.

6.2.2 Permitted Concomitant Therapy Requiring Caution

Anti-coagulant therapy is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin for > 2 weeks at time of first dose. International normalized ratio should be monitored as clinically indicated per investigator's discretion.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has previously occurred during infusions of IMCgp100 and monoclonal antibodies, [redacted]

6.2.3 Prohibited Concomitant Therapy

During the course of the study, patients may not receive other additional investigational drugs, agents, devices, anti-neoplastic therapy, or any other therapies that may be active against cancer. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study. [redacted]

[redacted]

6.3 Patient Numbering and Treatment Assignment

6.3.1 Patient Numbering

Each patient is identified in the study by a number that is assigned when the patient is first enrolled for Screening. The patient number is retained as the primary identifier for the patient throughout participation in the trial. The patient number consists of the center number assigned by the Sponsor and a sequential patient number suffix so that each patient is numbered uniquely across the entire database. Patient numbers will be assigned by the Sponsor at the time of Screening.

The subject number, patient ID along, with the last IMCgp100 dose and date of last dose from the parent study will be captured in the relevant eCRF for the rollover study.

6.3.2 Treatment Assignment

Patients enrolled in the rollover study will be assigned to the dosing regimen (please refer to Table 6-1, Section 6.1 Study Treatment) based upon the parent protocol in which the patient was enrolled and treated.

6.4 Study Drug Preparation and Dispensation

Further instructions for the preparation and dispensation of IMCgp100 are described in the Study Pharmacy Manual. See Section 6.1 Study Treatment for details.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.4.1 Packaging and Labeling of Study Drug(s)

Further instructions for the preparation and dispensation of IMCgp100 are described in the Study Pharmacy Manual. See Section 6.1 Study Treatment for details.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.4.2 Study Drug Compliance and Accountability

Study treatment will be administered to the patient by the trained study site staff at the study sites. Compliance with the prescribed regimen will be assured by administration of the study treatment under the supervision of investigator or his/her designee.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the site study monitor.

6.4.3 Drug Supply, Storage, and Disposal

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, IMCgp100 supply should be recorded and stored according to the instructions specified on the drug labels.

All IMCgp100 supply remaining at the end of the study, following appropriate drug accountability procedures at each site can be destroyed per local institutional practice at the study site or at a third party vendor as appropriate and agreed with Sponsor. Used vials can be discarded according to local procedures and recorded in the accountability log. Unused vials (after expiry or at the end of study) must be disposed of only after agreement from Sponsor and a certificate of destruction must be retained within the pharmacy binder.

6.5 Management and Follow-up of Toxicity

Patients whose study treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary for any AEs

observed in the course of the trial. In the case of a toxicity suspected to be related to a cytokine release syndrome, the immunologic assessments outlined in Section 7.3.4 should be performed.

Guidelines for management of AE and dose modifications are presented below in Table 6-2 (below). Institutional protocols for management of immune-related AEs should be implemented in cases of immune-related AEs and will take precedence over guidance in Table 6-2. All patients must be followed up for the occurrence of AEs and SAEs for 90 days following the last dose of IMCgp100.

[redacted]

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Table 6-2 Recommended Dose Modifications by Toxicity Grade for Study Medications

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Dose Modifications
Skin Toxicity	
Rash/Photosensitivity	
Grade 1	Continue dosing. If symptomatic, consider systemic antihistamine regimen
Grade 2	Hold all doses of study IMCgp100 until returned to NCI CTCAE grade ≤ 1. Use local skin management and systemic antihistamine regimen as indicated. **Anti-pruritic regimen:** Can include antihistamine therapy. In patients where antihistamine therapy does not provide adequate relief, gabapentin or aprepitant may be considered. **Topical corticosteroid regimens:** Preparation of recommended regimens • For face and/or intertriginous areas (including genitalia) recommend alclometasone 0.05% or hydrocortisone 2.5% creams • For other body areas (ie, trunk and extremities) recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation
Grade 3	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1.

Table 6-2 Recommended Dose Modifications by Toxicity Grade for Study Medications

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Dose Modifications
	Management: Treat according to institutional practice which generally includes an anti-pruritic regimen (see grade 2 management above). In addition, corticosteroid treatment (oral or topical) can be considered for symptomatic rash that does not respond to anti-pruritic regimen. For topical regimens, refer to grade 2 management above). **Dose adjustments:** If grade 3 rash observed with IMCgp100 resolves to NCI CTCAE grade ≤ 1 within 7 days, restart at the same dose. If grade 3 rash resolves to NCI CTCAE grade ≤ 1 in 7–21 days, restart with a reduction in the dose of IMCgp100, as discussed with the medical monitor.
Grade 4	Any grade 4 rash, permanently discontinue IMCgp100. Manage according to institutional practice, consultation with a dermatologist is recommended. All study medications must be permanently discontinued.
Infusion Reactions	
Grade 1	Administer medications for symptomatic relief as needed. Infusion interruption may be considered until resolution of the event (up to 4 hours). The infusion rate of the study medication may be decreased by 50%. If resolved with decreased rate of infusion, any subsequent infusions can be administered at the reduced rate.
Grade 2	Stop infusion and keep intravenous line open. Treat according to institutional practice. Provide all supportive measures as indicated. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (eg, blood pressure, pulse, and temperature) until resolution. Administer medications for symptomatic relief as needed. Antihistamines, acetaminophen (paracetamol), or corticosteroids may be administered, as needed at the discretion of the investigator. Restart infusion only once infusion reaction resolves (within 4 hours of initial start of infusion). Administer oral pre-medication (eg, 1000 mg of acetaminophen or paracetamol, 50–100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion. If the adverse event recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then permanently discontinue the patient from study treatment.
Grade 3 or 4	Discontinue infusion immediately, and permanently discontinue patient from study treatment. Manage severe infusion-related reactions per institutional standards. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (eg, blood pressure, pulse, respiration, and temperature) until resolution.
Hypotension	

Table 6-2 Recommended Dose Modifications by Toxicity Grade for Study Medications

Worst Toxicity NCI CTCAE v4.03 Grade	Recommended Dose Modifications
Grade 2	Intravenous fluid support and other supportive measures for additional AE as needed.
Grade 3 or 4	Hold all doses of IMCgp100 until returned to NCI CTCAE grade ≤ 1. Intravenous fluid support and other supportive measures for additional adverse events. In cases of hypotension where fluid support is not adequate, consider systemic corticosteroid therapy as needed for hypotension. In case of hypotension not responding to intravenous corticosteroid, inotropic pressor support may be indicated.
Cytokine Release Syndrome	
Grade 2	Interrupt infusion of IMCgp100. Supportive measures for symptoms of cytokine release, ie, intravenous fluid support, non-steroidal anti-inflammatory drug (NSAID), antihistamine. If resolves within 4 hours, may restart infusion of IMCgp100. If recurs with restarting infusion, hold the dose of IMCgp100 and institute supportive measures as indicated.
Grade 3	Discontinue infusion immediately. Supportive measures for symptoms of cytokine release, ie, intravenous fluid support, NSAID, antihistamine. To consider intravenous corticosteroid (eg, methylprednisolone or hydrocortisone) for severe symptoms and management of sequelae. If symptoms resolve to NCI CTCAE grade 1 within 7 days, may consider restarting IMCgp100 after written approval of Sponsor Medical Monitor.
Grade 4	Discontinue infusion immediately. Supportive measures for symptoms of cytokine release. In addition to supportive measures, intravenous corticosteroid dosing (eg, methylprednisolone or hydrocortisone) should be administered. If symptoms do not resolve with intravenous corticosteroid dosing consider anti-IL6 (tocilizumab) therapy. If symptoms resolve to NCI CTCAE grade 1 within 7 days, may consider restarting IMCgp100 after written approval of Sponsor Medical Monitor.
Other Adverse Events	
In patients experiencing adverse events (not meeting the specific criteria above) of grade ≥ 3, study drugs should be omitted until resolved to grade ≤ 1. Treat according to institutional practice and for immune-related adverse events of grade 3 or greater, treatment with corticosteroids should be considered. Consult Sponsor Medical Monitor for further guidance as needed.	

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory drug.

All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than 2 dose reductions should discontinue treatment.

6.6 Treatment Discontinuation

Reasons for discontinuation of study treatment will include:

- Unequivocal PD, see Section 6.6.1
- Loss of clinical benefit from treatment with IMCgp100 in the opinion of the principal investigator or the initiation of alternative anti-cancer therapy (including another investigational agent)
- Unacceptable toxicity defined as an AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing, including ≥ grade 3 cytokine release syndrome
- Withdrawal of consent from further treatment with investigational product by the patient or the investigator or lost to follow-up
- Patient is determined to have failed to meet selection criteria for the study AND continuing to receive investigational product might constitute a safety risk. Patients who fall into this category and for whom continuation of study treatment is not thought to pose a safety risk in the opinion of the investigator may continue to receive study treatment after discussion with the Sponsor
- Pregnancy or intent to become pregnant

At the time patients discontinue study treatment, the EOT visit should be scheduled in the appropriate window of 14 days after the last dose was administered. At this visit, all of the assessments listed for the EOT visit will be performed (see Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit (EOT follow-up will still continue for the full 14-day observation period, see Section 7.2 for details of assessments required). An End of Treatment eCRF page should be completed at the EOT visit, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of the study.

6.6.1 Criteria for Treatment Beyond Initial RECIST v.1.1 Disease Progression

Imaging studies will be performed on all patients to monitor for disease progression using RECIST v1.1 criteria. Upon disease progression by standard RECIST v.1.1 criteria, treatment beyond progression is an option.

Clinical evidence suggests that a minority of patients treated with immunotherapies, including IMCgp100, will derive clinical benefit after an initial assessment of PD. For patients in the IMCgp100 arm, if PD based on RECIST v.1.1 occurs, treatment may continue according to the protocol-specified regimen until 1 of the following criteria is met:

1. Unequivocal, confirmed PD based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (guidelines based on Wolchok, 2009; Nishino, 2013; and Bohnsack, 2014): An initial assessment of PD by RECIST v.1.1 (initial PD assessment) will be confirmed with a repeat radiologic evaluation will be performed at least 4 but no more than 12 weeks later as scheduled per protocol. For patients who continue IMCgp100 therapy beyond initial PD, unequivocal, confirmed PD is defined as an additional 20% increase in tumor burden (sum of diameters of both target and new lesions) from the initial PD assessment

2. Meets any of the investigational product discontinuation criteria (Section 6.6 above)

3. Clinical symptoms or signs indicating clinically significant PD (not meeting radiologic PD) such as decline in ECOG performance status or the benefit-risk ratio of continuing therapy is no longer justified

4. Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention

Once unequivocal, confirmed PD is recognized, treatment with IMCgp100 must be discontinued.

Patients continuing treatment beyond the protocol-specified RECIST v.1.1 progression must provide separate consent to continue treatment after an initial assessment of PD. Treatment and assessments after an initial assessment of PD will continue to follow the treatment regimen of weekly IMCgp100.

6.7 Contraception

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 6 months after the last dose of IMCgp100.

Highly effective contraception methods include and of the following:

- Total abstinence from sexual relations for the duration of the treatment when applicable to the lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient

- The combination of any 2 of the following methods as long as they are both used simultaneously:

    a. Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

    b. Placement of an intrauterine device or intrauterine system

    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) when used with spermicidal foam, gel, film, cream, or used of a spermicidal vaginal suppository

In case of use of oral contraception women should have been stable on the same oral contraceptive pill for a minimum of 3 months before beginning treatment on this study.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

7 STUDY SCHEDULE AND ASSESSMENTS

7.1 Screening Procedures and Assessments

All of the assessments required as part of the study are indicated in Table 7-1 organized by visit date, with assessments required indicated with an "X" at the specific visits when they should be performed. Laboratory and radiological assessments performed as part of the parent study and/or standard of care prior to signing the rollover informed consent may be used if performed within the screening time window (21 days for laboratory assessments). No radiologic assessments will be collected as part of the rollover study. Assessments performed as part of the parent study should be included in the parent study database. Please note, if the last dose of IMCgp100 on the parent study and the first dose of IMCgp100 on the rollover study are separated by more than 21 days, the first dose of IMCgp100 must be administered with overnight inpatient monitoring; given the risk of severe infusion-related toxicity and potential for hypotension (refer to Section 1.4 for details of clinical experience with IMCgp100).

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of ± 7 days is allowed unless otherwise indicated in the protocol.

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase									Follow-up Phase	
Procedure	**Protocol Section**	**Screening[a]**	**Rollover Cycle 1**				**Rollover Cycle 2**				**End of Treatment**	**90-day Safety Follow Up**	**Survival Follow Up**
			Day 1[a]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**			
Informed Consent	7.1.1	X											
Demography	7.1.1.2	X											
Inclusion/exclusion criteria	5.2/5.3	X											
Medical history	7.1.1.2	X											
Diagnosis and extent of cancer	7.1.1.2	X											
Prior/concomitant medications	7.1.1.2	X	Continually assessed										
Physical examination[b]	7.3.1	X	X	X	X	X	X	X	X	X	X		
Height	7.3.3	X											
Weight	7.3.3	X	X				X				X		
Vital signs[c]	7.3.2	X	X	X	X	X	X	X	X	X	X		
Hematology panel[d]	7.3.4	X	X	X	X	X	X	X	X	X	X		
Chemistry panel[e]	7.3.4	X	X	X	X	X	X	X	X	X	X		
Cytokine panel[f]	7.3.4		In case of a suspected cytokine release syndrome										
Pregnancy test[g]	7.3.4	X					X				X		
12-lead electrocardiogram	7.3.4	X									X		
IMCgp100 administration[h]	6.1		X	X	X	X	X	X	X	X			
Immunogenicity sampling[i]	7.3.5		X								X		
Adverse events	8	Continually assessed											
Tumor evaluation per RECISTv.1.1 and modified irRECIST (Refer to Section 6.6.1)	6.6.1	X	Assessed at a minimum of 12 week intervals										
Survival contact	7.2.4												X

Table 7-1 Schedule of Study Assessments

		Screening Phase	Treatment Phase									Follow-up Phase	
Procedure	**Protocol Section**	**Screening[a]**	**Rollover Cycle 1**				**Rollover Cycle 2**				**End of Treatment**	**90-day Safety Follow Up**	**Survival Follow Up**
			Day 1[a]	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**			

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors.

a. Screening and Rollover Cycle 1 Day 1 (RC1D1) may be the same day, no procedures or events need to be repeated.
b. At Screening (or RC1D1), prior to IMCgp100 infusion, a complete physical examination will be performed. From RC1D8 onwards, a short physical examination will be performed. See Section 7.3.1.
c. Frequent vital signs, as per institutional standard, should be implemented during any required inpatient observations at a minimum of every 4 hours. (Refer to Section 7.3.2 for additional details).
d. Hematology panel should be obtained at Screening, before every IMCgp100 dose, and at the End of Treatment visit as well.
e. Chemistry panel should be obtained at Screening, before every dose of IMCgp100, and at the End of Treatment visit.
f. Cytokine panel should be obtained in all patients with a suspected occurrence of cytokine release syndrome. See Section 7.3.4.
g. Pregnancy testing is required in all females of childbearing potential. At Screening, a serum pregnancy test must be performed within 72 hours before the first dose of IMCgp100. During the study (Day 1 of each cycle starting with Cycle 2) a serum or urine pregnancy test must be performed. At End of Treatment, a serum or urine pregnancy test must also be performed.
h. Please refer to Section 6.1 Study Treatment for details of **weekly** IMCgp100 administration.
i. Immunogenicity samples are to be taken at Day 1 of all odd-numbered cycles and at End of Treatment. All samples are to be collected immediately before IMCgp100 infusion.
j. Target and non-target tumors to be assessed for radiographic disease progression by modified irRECIST criteria (refer to Section 7.3.5). Disease assessment to be performed at a minimum of 12 week intervals.

7.1.1 Screening Assessments

The study IRB/IEC-approved informed consent form (ICF) must be signed and dated before IMCgp100 administration per the rollover study.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments required at Baseline will be performed. For details of all screening assessments, refer to Table 7-1. Screening assessments must be repeated if performed outside of the specified screening window.

7.1.1.1 Information to be Collected on Screening Failures

The demographic information, informed consent, and screening pages (with reason for screen fail) must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during Screening, which would be reported in the usual manner via eCRF AE page (See Section 8.4). If the patient is still enrolled in the parent study at the time of Screening and experiences an SAE, this SAE must be reported to both this rollover study, as well as the initial parent study (see Section 8.1 Assessment of Safety).

A patient who signed the Main Study ICF but failed to be started on study treatment for any reason will be considered a screen failure. If patients are found not eligible after signing the main study consent, the patients will be considered as screening failures, and data will be handled in the same manner.

7.1.1.2 Patient Demographics and Other Baseline Characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of cancer, prior/concomitant medications, prior procedures, significant non-drug therapies, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. Prior anti-neoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Anti-neoplastic Therapy eCRF during Screening.

7.2 Treatment, Treatment Discontinuation, and Follow-up Phases

7.2.1 Treatment Period

A treatment cycle is defined as 4 weeks for the purposes of scheduling procedures and evaluations. Please refer to Table 7-1 for details of the timing of required assessments and visit windows.

7.2.2 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make every effort to determine the primary reason for this decision and record this information in the patient's chart and

on the appropriate eCRF pages. Other reasons for discontinuation of study treatment are outlined in Section 6.6.

Patients will be considered withdrawn from treatment if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An end of treatment eCRF page should be completed, giving the date and reason for stopping the study treatment. End of treatment/premature withdrawal visit is not considered as the end of the study.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7 and Table 7-1 and be followed for the 90-day Safety Follow-up Period at a minimum. If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, email, postal letter) should be made to contact them. At this time, the reason for study completion should be recorded on the Study Disposition eCRF page.

7.2.3 90-day Safety Follow-up Period

All patients must have safety evaluations 90 days after the last dose of study treatment. Information related to all AEs (including concomitant medication taken for ongoing AEs) will be collected for 90 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up weekly or as clinically indicated until resolution or stabilization.

7.2.4 Survival Follow-up Period

Upon completion of the 90-day follow-up, patients will be followed for survival every 3 months (can be done by telephone call) until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up.

7.2.5 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family, or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, eg, dates of telephone calls, registered letters, etc, a patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Patient Disposition eCRF.

7.3 Safety and Tolerability Assessments

Safety will be monitored by assessing physical examination, vital signs, body height and weight, hematology, chemistry, pregnancy, ECG, cytokine testing, as well as collecting of the AEs at every visit. For details on AE collection and reporting, refer to Section 8, Adverse Events and Safety Reporting.

7.3.1 Physical Examination

Physical examination will be performed according to Table 7-1.

At Screening (or RC1D1), prior to IMCgp100 infusion on the rollover study, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From RC1D8 onwards, a short physical examination will be performed as indicated in the Schedule of Events, Table 7-1. A short physical exam will include the examination of general appearance, vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) and body sites as directed by symptoms.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the AE eCRF page.

7.3.2 Vital Signs

Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) must be performed before dosing, and after the IMCgp100 administration (at least twice after administration) as indicated in Table 7-1, and as per institutional standards. Clinically significant abnormalities are to be reported on the AE eCRF page.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator if medically indicated.

Frequent vital signs, as per institutional standard, should be implemented during any inpatient observations at a minimum of every 4 hours. If the full 21-day screening period is utilized for a patient, and the patient has a gap of greater than 21 days between their last dose of IMCgp100 on the parent study, and the first dose of IMCgp100 on the rollover study, the first dose of IMCgp100 (RC1D1) must be administered with overnight inpatient monitoring.

Patients experiencing a grade 3 or 4 hypotension event during any dose of IMCgp100 will require inpatient hospitalization for the next 2 doses. Further inpatient hospitalizations are at the discretion of the investigator.

Patients receiving IMCgp100 as an outpatient, for whom no grade 3 or 4 hypotension event was observed, should be monitored in the clinic for a minimum of 1 hour after the IMCgp100 infusion with at least 2 post-dose vital signs measurements performed.

7.3.3 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

7.3.4 Laboratory Evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally. Refer to Table 7-3 for a summary of the parameters to be evaluated according to Table 7-1. On dosing days of IMCgp100, samples for these parameters will be collected prior to the infusion of IMCgp100.

More frequent evaluations may be performed at the investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

The Sponsor or the designated contract research organization (CRO) will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor or the CRO must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-3 Local Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	Albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, calcium, chloride, creatinine, glucose magnesium, inorganic phosphate, potassium, sodium, total bilirubin (also measure direct and indirect bilirubin if total bilirubin is > grade 1), blood urea nitrogen or urea, amylase, and lipase
Cytokines	[redacted]

Hematology: The panels outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

Clinical chemistry: The panels outlined in Table 7-3 will be performed as per the assessment schedule in Table 7-1.

Cytokine analysis panel: The cytokine panel outlined in Table 7-3 will be performed on an as needed basis in case a patient has an AE suspected to include cytokine release syndrome. This assessment should be performed at the following time points:

- [redacted]
- [redacted]

Pregnancy and assessment of fertility: Pregnancy tests will be performed for women of child bearing potential. At Screening, a serum pregnancy test must be performed within 72 hours before the first dose of IMCgp100. During the study (Day 1 of each cycle starting with Cycle 2), a serum or urine pregnancy test must be performed. At EOT, a serum or urine pregnancy test must also be performed. Pregnancy will be reported through the Pregnancy Reporting Form (paper) as well as in the eCRF as an AE.

Cardiac assessments: A standard 12-lead ECG will be performed as per the assessment schedule in Table 7-1. ECG assessment is performed at Screening prior to the first dose and at EOT assessment. Clinically significant abnormalities present at Screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF page.

7.3.5 Immunogenicity Assessments

The immunogenicity blood samples should be taken according to Table 7-1. Details are also described in the laboratory manual for the handling, labelling, and shipment of immunogenicity blood samples. The blood samples should be collected immediately before IMCgp100 infusion, and it is essential that the actual time and date of collection be recorded on the patient's eCRF.

8 ADVERSE EVENTS AND SAFETY REPORTING

8.1 Assessment of Safety

All patients who receive any treatment with IMCgp100 will be considered evaluable for safety. All AEs, regardless of study drug relationship, will be collected through the 90-day Safety Follow-up Period. At the time of consent, if any patient has any ongoing AE(s) from the parent IMCgp100 study, the AE(s) will be captured on the eCRF page and the "Ongoing at Start of Study" must be answered "Yes". The start date recorded in the eCRF for the rollover study should be equal to the start date of the event as recorded in the parent study. Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and is mandated by regulatory agencies worldwide. The Sponsor and CRO have established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information. All clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Individual AEs should be evaluated by the investigator and should be reported to the CRO/Sponsor for evaluation. This includes the evaluation of the event's seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the AE. The CRO/Sponsor is required to maintain detailed records of all AEs reported by the investigator(s) and to perform an evaluation with respect to seriousness, causality, and expectedness. On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor should submit detailed records of all AEs which are reported by the relevant investigators. Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

8.1.1 Definitions

Definitions of AEs, adverse drug reactions, SAEs, unexpected adverse drug reactions, and AEs of special interest (AESI) are presented below.

AE: An AE is defined as the appearance of (or worsening of pre-existing) an undesirable sign, symptom, or medical condition that occurs after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication.

Adverse drug reaction: An adverse drug reaction is an unwanted or harmful reaction which occurs after administration of a drug or drugs and is suspected or known to be due to the drug. Adverse drug reactions have traditionally been categorized as pharmacologic (predicted based on the pharmacology of the drug) or idiosyncratic (not predicted based on pharmacology).

SAE: A SAE is any AE that is defined as 1 of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability or incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Death due to the progression of malignancy should not be reported as a SAE, if documented by use of appropriate method (eg, as per Response Evaluation Criteria in Solid Tumors v.1.1). Any AE that occurred as a result of the PD should be reported in the appropriate manner

Unexpected adverse drug reaction: An adverse drug reaction that is not consistent with applicable product information or characteristics of the study drug.

Suspected, unexpected, serious adverse reaction (SUSAR): A SUSAR is an adverse reaction meeting serious criteria (above), the nature or severity of which is not consistent with the reference safety information for the investigational drug(s).

AESI: An AESI (serious or non-serious) is an AE with scientific and/or medical concern specific to the Sponsor's program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Refer to the IMCgp100 Investigator's Brochures for details of the AESI.

8.2 Criteria for Expectedness

The concept of expectedness refers to events that may or may not have previously been observed and documented and not necessarily the known pharmacological properties of the medicine. An AE will be unexpected for purposes of regulatory reporting unless it is mentioned in the appropriate reference safety information within the current Investigator's Brochure for the investigational drug, even if it is a medical occurrence expected for the disease being treated.

8.3 Assessment of Causality

8.3.1 Causality Assessment Required for All Adverse Events

The investigator decides whether he or she interprets the observed AE as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terms are defined:

(1) Related: A direct cause and effect relationship between the study treatment and the AE is likely

(2) Possibly related: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible

(3) Unrelated: Without question, the AE is definitely not associated with the study treatment

All "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.4 Adverse Event Reporting

8.4.1 Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as serious are subject to expedited reporting. Expedited reporting of cases will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. Additionally, any safety information from other observations that could change the risk benefit evaluation of the product will be communicated in an expedited manner to the regulatory authorities and all investigators by the Sponsor.

The CRO will be responsible for the processing and reporting of SAEs. AEs will be coded by using International Conference on Harmonization (ICH) Medical Dictionary for Regulatory Activities.

Minimum criteria for a valid adverse drug reaction case have been established by ICH and individual regulatory agencies and are listed as the following:

- An identifiable reporter
- An identifiable patient
- A reaction/event
- A suspected medicinal product

Other safety issues that also qualify for expedited reporting by the Sponsor are those that would materially alter the current benefit risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial). Although these events will not be reported as SUSARs, they might require other action, such as putting in place urgent safety

measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and all IEC of safety issues which might materially alter the benefit-risk assessment of the investigational agents.

8.4.2 Standards for Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as SUSAR are subject to expedited reporting. Additionally, any safety information from other observations that could change the risk-benefit evaluation of the product should be promptly communicated to the regulatory authorities. Any other SUSAR associated with the investigational product should be reported as soon as the Sponsor becomes aware of them, and this includes SUSAR which occur in another trial conducted by the same sponsor or which are identified by spontaneous reports or a publication, or which are transmitted to the sponsor by another regulatory authority.

8.4.3 Reporting of Out-of-range Laboratory Test Results as Adverse Events

Out-of-range laboratory test results should be reported as AEs (not as abnormal laboratory values, ie, report as anemia, not low hemoglobin) if, in the opinion of the principal investigator, they are clinically significant. Abnormal laboratory results that are not considered to be clinically significant will not be reported as AEs. Significance of abnormal laboratory results should be documented in the study records.

8.4.4 Reporting Guidelines for Other Observations

Other safety issues that also qualify for expedited reporting where they might materially alter the current benefit risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial), for instance include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- A post-study SUSAR that occurs after the patient has completed a clinical trial and is reported by the investigator to the Sponsor

Events which occur during the trial and are relevant in terms of patient safety, but which do not fall within the definition of SUSAR (and thus are not subject to the reporting requirements for SUSARs) are:

- An SAE which could be associated with the trial procedures and which could modify the conduct of the trial
- A significant hazard to the patient population such as lack of efficacy of an investigational medicinal product
- A major safety finding from a newly completed animal study (such as carcinogenicity)

- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal product in another country by the same Sponsor

- Safety recommendations of the Safety Management Team

Although these events/observations will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and the IECs of safety issues, which might materially alter the benefit-risk assessment of the investigational medicinal product.

Expedited reporting is not usually required for reactions that are serious but expected, or for non-serious adverse reactions whether expected or not.

It is usually also inappropriate to report events that are considered unrelated to the investigational medicinal product.

8.4.5 Pregnancy Reporting

Pregnancy will be reported through the Pregnancy Reporting Form (paper) as well as in the eCRF as an AE. The Pregnancy form (paper) should be completed and reported as indicated to the CRO pharmacovigilance team within 24 hours of being made aware of the event. Women who become pregnant during the study will be withdrawn from treatment at the earliest opportunity. The investigator shall report all pregnancies immediately to the CRO. The CRO will then notify the Sponsor within 1 business day of being informed of the event. Following withdrawal from the study, every attempt will be made to follow the patient and any resulting offspring for up to 6-weeks postpartum, unless otherwise medically indicated. Abortion, stillbirth, or any malformation/disease in the offspring must be reported as an SAE.

For men participating in the study who report the pregnancy of a partner, the investigator will ask to collect information about the results of the pregnancy/birth using the Pregnant Partner forms. The partner may be asked to sign a consent form giving permission for information to be collected. This health information will become part of the research study records. It will be shared with the Sponsor.

8.5 Investigator's Responsibilities

The investigator is responsible for the collection of AE data. All AEs should be recorded in the eCRF. The investigator shall report all SAEs immediately within 24 hours of being made aware of the event to Pharmacovigilance via the clinical database by completing as much information as possible and checking Yes when prompted whether the event is classified as an SAE in the AEs eCRF. The initial reporting can be supplemented by written reports using the SAE report form provided.

The follow-up reports (if required) shall identify the trial patients by unique code numbers assigned to the patient. The investigator shall supply the Sponsor with any additional requested information, notably for reported deaths of a patient.

All SAEs that occur between obtaining the patient's informed consent and 90 days after the last dose of study drug must be reported promptly to the CRO not later than 24 hours after the investigators or co-investigators become aware of their occurrence using the SAE eCRF in the study database.

The SAE eCRF is accessed via the study database. The following minimum information is required for the report:

- Patient identification (patient number and date of birth)
- Trial number
- Study treatment (dose, route, form, regime, start date, end date)
- Concomitant medication (including dose, route, form, regime, start date where available)
- Nature of SAE (overall diagnosis where available or alternatively signs and symptoms)
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study treatment
- Outcome
- Identify the reporter
- Action in relation to study (withdrawn from treatment, suspended, none)

The investigators or co-investigators are required to sign the SAE submission electronically in the clinical database within 24 hours of awareness of the event, even if the required information is incomplete or if the investigators are awaiting laboratory or diagnostic reports. Investigators may be asked for additional information for any reported SAE. An SAE follow-up report with attached documents (if necessary) should be forwarded to CRO Pharmacovigilance as soon as the additional information is available by email. The study number IMCgp100-401 must be in the title of any email for study identification purposes.

8.6 Sponsor and Clinical Research Organization's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the investigational drugs being studied. The Sponsor and CRO are responsible for ensuring that expedited reports are made to all concerned investigators, to the IEC where required, and to all regulatory authorities of all adverse drug reactions that are both serious and unexpected, or findings that could adversely affect the health of patients, impact on the conduct of the trial, or alter the competent authority's authorization to continue the trial in accordance with local applicable regulations.

9 STATISTICAL METHODS AND DATA ANALYSES

9.1 General Principles

Data will be summarized using descriptive statistics. Categorical data will be presented as frequencies, medians, and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The following rules will be followed for reporting results unless stated otherwise:

- Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses, but will be reported in the clinical study report as separate listings
- Baseline is defined as the last assessment prior to the first dose of treatment received (ie, RC1D1 pre-dose)
- Additional analyses not described here will be detailed in the statistical analysis plan for the study

9.2 Analysis Sets

9.2.1 Full Analysis Set

The full analysis set (FAS) comprises all patients assigned to treatment, who received at least 1 full or partial dose of IMCgp100. The FAS will be used for all demography, baseline characteristics, and OS data summaries.

9.2.2 Safety Analysis Set

The safety analysis set includes all patients who have received at least 1 full or partial dose of IMCgp100. Patients will be classified in this set according to initial treatment received. The safety analysis set will be used for the safety summary of the study.

9.3 Patient Demographics and Other Baseline Characteristics

Demographic data, baseline disease characteristics, and other baseline data will be listed in detail. Quantitative data (eg, weight) will be summarized by appropriate descriptive statistics.

9.4 Treatment Data

Actual dose and duration in days of treatment for IMCgp100, as well as the dose intensity (actual dose received/actual duration), and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be summarized by descriptive statistics

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by anatomical therapeutic chemical term.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last doses, duration of exposure to each study drug, and date of discontinuation for each patient.

9.5 Primary Analysis

9.5.1 Variables

The primary variable is the incidence of AEs.

9.6 Secondary Analyses

9.6.1 Safety

For all safety analyses, the safety analysis set will be used.

The overall observation period will be divided into 3 mutually exclusive segments:

1. Pre-treatment period: From day of patient's informed consent to the day before first dose of study treatment
2. On-treatment period: From day of first dose of study treatment to 90 days after last dose of study medication
3. Post-treatment period: Starting at Day 31 after last dose of study treatment

9.6.1.1 Adverse Events

Summary tables for AEs include only AEs that are new or worsened during the on-treatment period (treatment-emergent AEs). However, all safety data (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent AEs will be summarized by system organ class and/or preferred term, severity (based on NCI CTCAE v.4.03 grades), type of AE, and relation to study treatment by treatment group. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

9.6.1.2 Laboratory Abnormalities

For laboratory tests covered by the NCI CTCAE version 4.03 the study team will grade laboratory data accordingly. For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and other laboratory:

- Frequency table for newly occurring on-treatment grades 3 or 4 and all grades
- Shift tables of laboratory and ECG data using NCI CTCAE grades to compare Baseline to the worst on-treatment value
- Listing of all clinically relevant laboratory data and relevant ECG data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges

9.6.1.3 Other Safety Variables

- Vital signs absolute values and changes from Baseline will be summarized. Normal ranges will be specified in the statistical analysis plan and shift tables of Baseline to worst on-treatment results will be produced
- ECG data: QTc interval absolute values and changes from Baseline will be summarized. Abnormalities will be classified according to NCI CTCAE grades and shift tables of Baseline to worst on-treatment results will be presented
- Physical examination data will be listed and abnormalities will be flagged

9.6.1.4 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

9.7 Exploratory Analyses

9.7.1 Overall Survival

Date of death will be collected to assess OS only and will be listed according to treatment regimen.

The OS data will be presented graphically via Kaplan-Meier survival curves.

9.7.2 Immunogenicity—Exposure and/or Adverse Event Relationship

[redacted]

9.8 Interim Analysis

No formal interim analyses are planned.

9.9 Sample Size Calculation

No formal sample sizing will apply to this study.

10 DATA HANDLING AND MANAGEMENT

10.1 Data Confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the protected health information that will be collected and the use or disclosure of that information. If the patient revokes authorization to collect or use this information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. To protect the health information of study patients, access to the data collection system will be controlled by a sequence of individual user identification codes and passwords that are made available only to authorized trained personnel.

10.2 Site Monitoring

Before study initiation at trial sites, Sponsor and/or CRO study team members will review the protocol and eCRFs with the investigators and the site study staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to good clinical practice (GCP), the progress of enrollment, and to ensure that study treatments are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. The investigator must assure that the site monitor is allowed access to all study files, including all site medical records, case and visit notes, and laboratory reports.

10.3 Data Collection

The investigator is required to maintain source documents for each patient in the study, consisting of case and visit notes (site medical records), containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded in the eCRF must be traceable to source documents in the patient's file. The investigator must also keep the original signed ICF, with 1 signed copy given to the patient.

This study will use an electronic data capture (EDC) system and the principal investigator and site study staff will enter the data required by the protocol into the eCRF. The eCRF have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. The principal investigator and all identified site staff will not be given access to the EDC system until they have been trained. The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. Field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions.

Field monitors will review the eCRF and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample by the site staff and 1 copy will be retained at the investigational site.

10.4 Database Management

Sponsor clinical study personnel and trial field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system.

Concomitant treatment and prior medication data in the database will be coded using the WHO Drug Reference List, based on the anatomical therapeutic chemical classification. Medical history, current medical conditions and AEs in the database will be coded using the Medical Dictionary for Regulatory Activities terminology. After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Study Documentation, Record Keeping, and Retention of Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine any clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded.

The investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and guidelines. The investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for a period of not less than 15 years from the completion of the clinical trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and guidelines.

11.2 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and Unites States Code of Federal Regulations, CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.3 Responsibilities of the Investigator and Institutional Review Board/Independent Ethics Committee/Research Ethics Board

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB or IEC or Research Ethics Board (REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to field monitors, auditors, CRO representatives, designated agents of the Sponsor, the IRB or IEC or REB, and regulatory authorities as required.

11.4 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he or she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures. The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be captured in the eCRF.

11.5 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 3.5 Early Study Termination.

11.6 Publication of Study Protocol and Results

The Sponsor will publish the key design elements of this protocol in a publicly accessible database (clinicaltrials.gov). At the time of study and clinical study report completion, the results of this study will be either submitted for publication and/or posted in a publicly accessible database.

11.7 Confidentiality of Study Documents and Patient Records

The investigator must ensure anonymity of the patients; patients must not be identified by name in any documents submitted to the Sponsor or the CRO. Signed ICFs and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and Inspections

Source data and all trial documents must be available to inspections by the Sponsor, the CRO or designee, or Health Authorities.

11.9 Financial Disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

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