1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E7046-G000-101
Study Protocol Title:	An Open-Label Multicenter Phase 1 Study of E7046 in Subjects With Selected Advanced Malignancies
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677, USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	E7046
Indication:	Multiple tumor types with high myeloid infiltrate
Phase:	Phase 1
Approval Date(s):	Original Protocol: 07 May 2015 Amendment 01: 30 Dec 2015 Amendment 02: 03 August 2016
IND Number:	125272
EudraCT Number:	2014-004823-37
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement:

This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Study Protocol Title

An Open-Label Multicenter Phase 1 Study of E7046 in Subjects With Selected Advanced Malignancies

Objectives

Primary objectives are to:

- assess the safety and tolerability of E7046
- determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of E7046.

Secondary objectives are to evaluate:

- pharmacokinetic (PK) profile of E7046.
- objective response rate according to the immune-related RECIST (irRECIST)
- time to response (TTR), duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and clinical benefit rate (CBR).

Exploratory objectives include:

- explore efficacy according to modified RECIST 1.1
- assess overall survival (OS)
- explore the pharmacodynamic effect of E7046 on selected immune cell populations and selected biomarkers in tumor infiltrate and in peripheral blood.
- explore ^{18}FDG-PET as a biomarker of response
- explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship.

Study Design

This is an open label, multicenter, Phase 1 study of E7046, a small molecule inhibitor of the prostaglandin E_2 (PGE_2) receptor type 4 (EP4). The study will be conducted in 2 parts: a dose escalation part to determine the MTD and/or RP2D of E7046, and a cohort expansion part with 6 to 16 subjects to better characterize safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) at the RP2D.

In the dose escalation part, increasing doses of E7046 will be administered to cohorts of 6 subjects, at dose levels ranging from 125 mg to 750 mg, (see Table below). In the first dose cohort, staggered dosing starts will be employed to ensure exposure of a limited number of subjects in initial dosing.

Dose level	No. of Subjects	E7046 Dose
-1	6	75 mg QD
1	6	125 mg QD
2	6	250 mg QD
3	6	500 mg QD
4	6	750 mg QD

Dose-limiting toxicities (DLTs) will be drug-related toxicities (considered related, probably related, or possibly related to E7046) and graded using NCI CTCAE 4.03 occurring during Cycle 1 and include:

- Nonhematologic toxicity ≥ Grade 3 (except diarrhea, nausea and vomiting unless lasting >3 days despite optimal supportive care)
- Confirmed (with a second measurement after 24 hours) nonhematologic appropriately-graded laboratory findings of Grade ≥3 that were ≤ Grade 1 at baseline
- Hematologic toxicity: Grade 4 neutropenia ≥ 5 days, or Grade 3 neutropenia with fever, Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or lasting >7 days
- Any other toxicity assessed as related to E7046 treatment, and which, in the opinion of the study investigator(s) and the sponsor physician constitutes a dose-limiting toxicity
- Missed ≥ 7 days of dosing in Cycle 1 due to drug-related toxicity (but not qualifying for a DLT).

The following toxicities will not be considered DLTs:

- Grade ≤3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade ≤3 immune-related adverse event (irAE) that resolves to Grade ≤1 within 7 days (see protocol body for definition of irAE)

Subjects who for reasons other than drug related toxicity or a DLT, fail to complete 75% of the planned total dose in Cycle 1, (equivalent to 16 out of 21 days) will be replaced.

The MTD is defined as one dose level below the dose level where ≥2 of 6 subjects experience a DLT. If ≤1/6 subjects in all dose cohorts experience a DLT, then an MTD will not have been reached. In this case, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, for all dose levels tested.

An expansion cohort of 6 to16 subjects will be enrolled to confirm the RP2D after completion of dose escalation part.

Study Population

This study will be conducted in subjects with tumor types that harbor high levels of myeloid infiltrate based on the Cancer Genome Atlas (TCGA), in keeping with the expected action of E7046 on intratumoral immunosuppressive cells of myeloid lineage.

Approximately 30 to 40 subjects will be enrolled, 24 in the dose escalation part, and 6 to 16 subjects in the cohort expansion.

Study Treatment

E7046 will be administered as a single agent orally once daily (QD) continuously in 21-day cycles. Subjects will be required to fast 2 hours before and 2 hours after the E7046 dose.

Subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, withdrawal of consent or termination of the study program.

Study Assessments

Efficacy Assessments

Tumor assessments will be performed by investigators based on both irRECIST and modified RECIST 1.1; however, the treatment decisions will be based on irRECIST. Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks.

Pharmacokinetic Assessments

Blood samples for PK analyses will be collected during Cycle 1 on Day 1 and Day 8 at predose (0 h), 0.5, 1, 2, 4, 6, 8, and 10 and 24h postdose. Urine samples for PK analyses will be collected during the Dose Escalation part only during Cycle 1.

The major metabolite identified in nonclinical species (M1) will also be analyzed.

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/MUGA scans, electrocardiograms (ECGs), and physical examinations. The effects of E7046 on cardiovascular repolarization will be evaluated via continuous Holter/ECG monitoring. Subjects with decreasing hemoglobin levels or gastrointestinal symptoms indicative of gastrointestinal bleed should be evaluated for a potential gastrointestinal bleeding source as appropriate.

Statistical Methods

The sample size of 30 to 40 subjects is considered adequate for the purposes of selecting RP2D. The expected sample size for the dose escalation part of this trial will be up to 24 subjects Per the dose escalation design adopted and modified from the traditional 3+3 design (see protocol body), there will be a maximum of 4 planned cohorts and there will be 6 subjects in each cohort to allow for adequate assessment of tolerability, clinical benefit, PK, PD data and integrated evaluation of safety so as to select RP2D.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

Efficacy parameters including ORR, response duration, time to response, PFS, DCR, and CBR will be listed and descriptively summarized as appropriate. For response duration and time to response, summary statistics (median Q1, Q3, and range) will be summarized for subjects achieving a best overall response of confirmed partial or complete response.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BP	blood pressure
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CRA	clinical research associate
CRC	colorectal cancer
CRF	case report form
CSF 1R	colony-stimulating factor-1 receptor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EP_4	prostaglandin E_2 (PGE_2) receptor type 4
FDA	Food and Drug Administration
^{18}FDG-PET	^{18}fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

irAE	immune-related adverse event
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRECIST	immune-related Response Evalution Criteria Criteria in Solid Tumors
irSD	immune-related stable disease
IRB	Institutional Review Board
LVEF	left ventricular ejection fraction
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease, or pharmacodynamic(s)
PFS	progression-free survival
PGE_2	prostaglandin E_2
PK	pharmacokinetic(s)
POP	Proof of Principle
PR	Time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex
PT	preferred term
QD	once daily
QRS	Time taken for depolarization of the ventricles
QT	Time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QTc corrected for heart rate by the Friderichia method
RECIST	Response Evaluation Criteria In Solid Tumors

RP2D	recommended Phase 2 dose
SAP	statistical analysis plan
SAE	serious adverse event
SCCHN	squamous cell carcinoma of head and neck
SOC	system organ class
ssIR	suspected severe immune reaction
SUV	standardized uptake value
TAM	tumor-associated macrophages
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate (CRA), change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable AEs per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome. It is expected that the study duration will be 18 months.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2008
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- A waiver from the IRB(s)/IEC(s) will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and

explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations and provided to the sponsor. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 3 investigational site(s) in the USA and potentially other locations globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 E7046 Background

7.1.1 E7046 Mechanism of Action

E7046 is a small molecule compound that is a specific inhibitor of the prostaglandin receptor EP_4 (Figure 1). Prostaglandins play a key role in mediating inflammatory responses, and their effects on differentiation of monocytic cells have been subverted by tumors to maintain an immunosuppressive tumor microenvironment (Qian and Pollard, 2010; Heusinkveld and van der Burg, 2011; Highfill, et al., 2014).

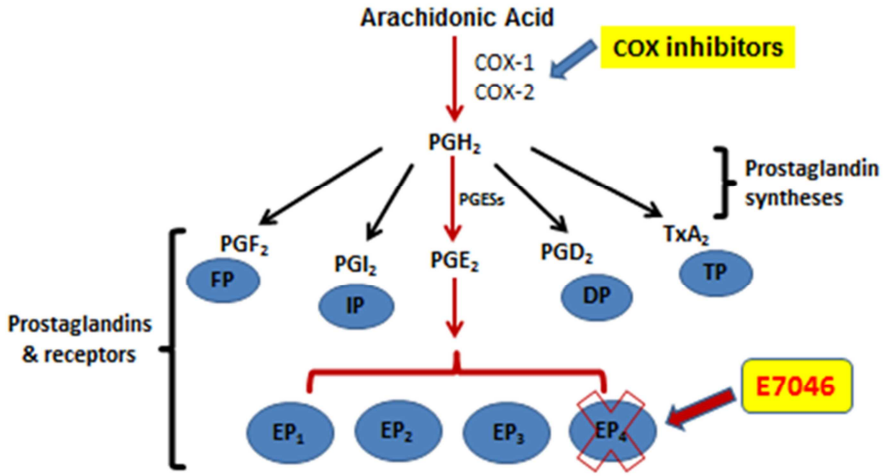


Figure 1 Molecular Target for E7046 and Arachidonic Acid Cascade

E7046 is a selective EP_4 antagonist. The molecular targets for the COX inhibitors are also shown for comparison. COX = cyclooxygenase, DP = prostaglandin D_2 receptor, EP_4 = prostaglandin E_2 receptor 4, FP = prostaglandin $F_{2\alpha}$ receptor, IP = prostacyclin receptor, PG = prostaglandin, PGES = prostaglandin E synthase, PGI_2 = prostacycline, TP = thromboxane receptor, TxA_2 = thromboxane A_2.

Through selective antagonism of EP_4, which is one of the four known receptors for the prostaglandin PGE_2, E7046 inhibits the differentiation and function of intratumoral monocytic myeloid lineage cells. These target cells, which include tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSCs), contribute to the formation and maintenance of an immunosuppressive tumor microenvironment. E7046 thus acts to relieve tumor suppression of T-effector cells (Figure 2) (Baum, et al., 2013). This concept has been supported by preclinical experiments using a variety of genetic, cellular and molecular approaches, and animal models, in conjunction with the Cancer Genome Atlas (TCGA) cancer bioinformatics to identify tumor types with high level of myeloid infiltrate. This mechanism of action is distinct from the T cell-targeting action of the immune checkpoint inhibitors (eg, ipilimumab CTLA4 antibody, and PD1/PDL1 antibodies) that have shown recent success in the clinic (Hodi, et al., 2010; Topalian, et al., 2012; Robert, et al., 2014) (Figure 2).

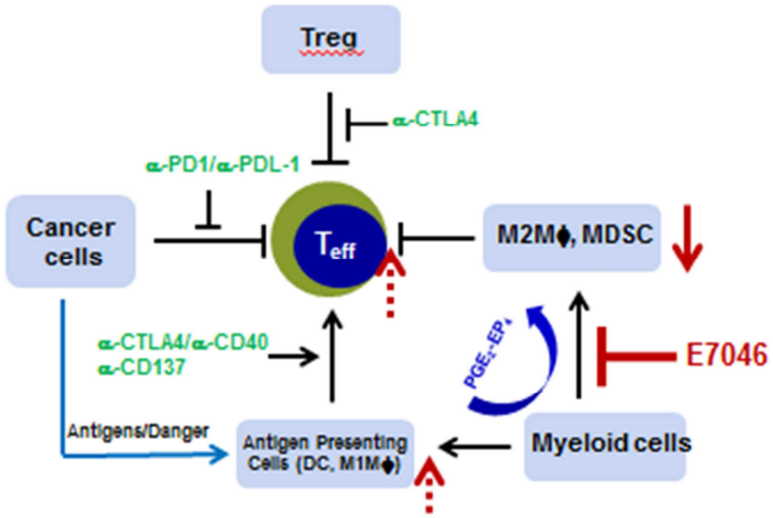


Figure 2 E7046 modulates immunosuppressive myeloid cells for cancer immune therapy

E7046 inhibits the formation and function of immune suppressive M2Mϕ and MDSC by antagonizing EP_4 signaling in myeloid cells. Consequently, formation of antigen-presenting cells (DC and M1Mϕ) were increased to promote T effector cell (T_{eff})-mediated antitumor adapative immune response. Drugs (approved of in development) that affect the different pathways are indicated.
DC = dendritic cells, MDSC = myeloid-derived suppressor cell, M1Mϕ = M1 macrophage, T_{eff} = T effector cells, Treg = regulatory T cells.

7.1.2 Therapeutic Indication

E7046 is intended to be developed as a new type of cancer immune therapy targeting host immunosuppressive cells in the tumor microenvironment that are of myeloid lineage.

Tumor types that will be explored include pancreatic adenocarcinoma, renal clear cell carcinoma, squamous cell carcinoma of head and neck (SCCHN), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), serous epithelial ovarian cancer, cervix cancer, transitional cell bladder cancer, and triple-negative breast cancer (TNBC).

7.1.3 Preclinical Summary

7.1.3.1 Pharmacology

E7046 selectively inhibits binding of PGE_2 to human EP_4 and thus inhibits PGE_2-EP_4 mediated cellular signaling. Activity of E7046 is dependent on the presence of intact immune system. E7046 did not show any antiproliferative activity towards cancer cells in vitro; however, daily oral administration of E7046 in immunocompetent mice showed significant in vivo antitumor activity against multiple models of syngeneic murine tumors rich in myeloid cells. No such antitumor activity was observed in tumors that were growing in immunodeficient nude mice or in immunocompetent mice bearing syngeneic tumors with few infiltrating myeloid cells.

Treatment of tumor-bearing animals with E7046 significantly altered the populations and functions of immune cells, both in the tumors and in the periphery. Furthermore, in mouse syngeneic tumor models, the combination of E7046 with radiation, with radiation plus gemcitabine, or with immune checkpoint blockade agents such as anti-CTLA4 antibodies all showed significantly better antitumor activity compared with radiation, radiation plus gemcitabine, or immune checkpoint blockade agent alone. E7046 is thus considered a novel cancer immune therapy that has potential therapeutic effects in multiple human tumor types.

7.1.3.2 Pharmacokinetics and Metabolism

Pharmacokinetic (PK) profiles of E7046 after oral administration in mouse, rat and dog were characterized by fast absorption (median t_{max} range: 0.25-0.75 h), extensive distribution (mean V_{ss} range: 3.85-7.18 L/kg), slow clearance (mean CL range: 0.27-1.35 L/h/kg), and slow elimination ($t_{1/2}$ range: 3.60-19.17 h).

Bioavailability was moderate to high in all three species (%F range: 31.2 %-82.3 %) and was the highest in dogs. An enterohepatic circulation of E7046 was observed in both rat and dogs. Plasma protein binding of E7046 was 50% to 70% and constant within the range of concentrations tested (200 to 20000 ng/mL) in mouse, rat, dog, monkey, and human. The C_b/C_p ratio across species was approximately unity (≤ 1) suggesting an equal distribution between plasma and blood cells.

The major metabolite of E7046 was identified as an acyl-glucuronide of E7046 (ER-000888188-000) from cryopreserved hepatocytes of human, mouse, rat, beagle dog and monkey. No human- unique metabolite was found. The main elimination path of E7046 in rats was via biliary excretion, while the renal clearance was a minor pathway in both rats and dogs.

The potential of CYP-mediated drug-drug interaction is predicted to be insignificant as E7046 showed neither CYP induction activity nor inhibition of any of the major CYP enzymes. E7046 did show weak time-dependent inhibition (TDI) of CYP3A.

Human E7046 doses of 20 mg/man/day and 200 mg/man/day is predicted to sustain unbound drug concentration above human EP_4 IC_{50} and IC_{90}, respectively. In all mouse pharmacology models tested, 50 mg/kg was an effective antitumor dose. This corresponds to an equivalent human dose of 120 mg/man/day, which is a dose sustaining drug concentration of between IC_{50} and IC_{90} for human EP_4.

7.1.3.3 Toxicology and Safety Pharmacology

Toxicity of E7046 was evaluated in single- and repeated-dose oral toxicity studies in male and female rats and dogs (up to 4 weeks). E7046 induced similar toxicities across preclinical species. Major findings in dogs and rats were limited to dose-dependent intestinal effects and testicular toxicity. Intestinal changes were characterized by abnormal stools which resulted in progressive weight loss at highest dose tested. In addition, E7046 induced minor changes in heart rate and blood pressure (BP) in the dog at exposures more than 2 fold higher than the predicted efficacious human exposure.

The proposed starting dose in humans of 125 mg is less than 1/9 of the human dose equivalent in dogs that caused only occasional mucous stool and slight testicular changes. If translated into the clinic, both would be considered acceptable changes in the intended subject population. Based on the observed toxicities in preclinical species, E7046 may cause the side effects in humans including, but not limited to, the following:

Gastrointestinal system: Colitis, characterized by new onset of diarrhea, which may be accompanied by abdominal pain and or gastrointestinal bleeding.

Testicular system: Decreased testicular weight, hypo cellularity.

Cardiovascular system: Reversible increase in heart rate and decrease in mean blood pressure.

Safety pharmacology of E7046 was evaluated in vitro for hERG channel inhibition and platelet aggregation, in vivo for cardiovascular function in dogs, and for respiratory and central nervous system functions and prostanoid metabolism in rats. No significant adverse effects of E7046 were observed in these studies except for an increase in heart rate, and a decrease of BP at 100 mg/kg of E7046 in dogs. Low risk of side effects in cardiovascular, respiratory and central nervous system is anticipated for E7046 in humans.

Preclinical safety studies thus suggest that E7046 has an acceptable safety profile in the intended population at proposed clinical doses.

7.2 Study Rationale

The interaction between cancer cells and the tumor microenvironment is complex, but recent research has begun to reveal the mechanisms by which a successful tumor embeds itself within a network of supporting normal cells, such that targeting the tumor microenvironment is at the forefront of developments in novel cancer therapy (Hanahan and Weinberg 2011). The human immune system is empowered to fight foreign antigens by a continuous surveillance around the whole body. Though immune cells are able to impair early tumor development in most people, in cancers that reach clinical attention, the immune system has become immune tolerant of the tumor tissue at both local and systemic levels (Schreiber, et al., 2011**).**

An approach to effectively break immune tolerance in cancer subjects holds the key to successful cancer immune therapy. Recent Food and Drug Administration (FDA) approval of two cancer immune therapies that specifically target cancer-hijacked immune support systems, anti-CTLA4 (Yervoy®; ipilimumab) and dendritic cells modified ex vivo (Provenge®; sipuleucel T), exemplified this trend. Several additional therapies targeting the immune components of the tumor microenvironment (eg, nivolumab) are currently in clinical trials with very promising clinical effects (Brahmer, et al., 2012; Topalian, et al., 2012).

Immunosuppressive signals come from cancer cells as well as immune cells (Figure 2). CTLA4 blockade inhibits the suppressive signals from effector T cells (cytotoxic T cells and Th1/2 cells) themselves and from Treg cells, while PD1/PDL1 blockade mainly inhibits the signals from cancer cells (Brahmer, et al., 2012; Topalian, et al., 2012). Another immunosuppressive mechanism in the tumor microenvironment is supplied by myeloid cells. Myeloid cells respond to signals in their local environment by acquiring a phenotype that is appropriate for the condition. These phenotypes are considered either type 1 (M1Mϕ), which are pro-inflammatory, antimicrobial and antitumor antigen-presenting macrophages, or type 2 (M2Mϕ), which are pro-angiogenic, anti-inflammatory, immunosuppressive wound-healing MDSC and TAM.

The presence or accumulation of TAM and MDSC cells in tumors is well documented in the literature to be associated with a poorer prognosis in many types of human carcinomas and adenocarcinomas, including colon, pancreatic, lung, breast, head and neck squamous cell (HNSSC), prostate, hepatocellular carcinoma (HCC) and colorectal (CRC), thyroid, melanoma and others (Joyce and Pollard, 2009; Ganjoo, et al., 2011; Medrek, et al., 2012; Zhang, et al., 2012).

Due to its exquisite receptor selectivity, oral bioavailability, strong preclinical safety profile, and unique antitumor mechanism, E7046 is an excellent candidate to be developed as a novel anticancer immune therapy by targeting immunosuppressive TAM/MDSC. Treatment with E7046 is intended to modify the immunosuppressive tumor microenvironment by inhibiting the accumulation of MDSC and TAM, and thus permitting enhanced host immune responses against the tumor.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objective of the study is to:

- Assess the safety/tolerability profile of E7046 as a single agent administered orally once daily, continuously in 21-day cycles, in subjects with selected advanced and/or recurrent malignancies.
- Determine the MTD and/or RP2D of E7046.

8.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the pharmacokinetic (PK) profile of E7046.
- Evaluate the ORR according to immune-related RECIST (irRECIST) in subjects treated with E7046 with selected tumor types with high level of myeloid infiltrate
- Evaluate the following additional efficacy endpoints according to irRECIST: time to response (TTR), duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and clinical benefit rate (CBR).

8.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Explore efficacy according to modified RECIST 1.1, using the following endpoints: ORR, TTR, DOR, PFS, DCR, and CBR
- Assess overall survival (OS)
- Explore the pharmacodynamic effect of E7046 on selected immune cell populations and selected biomarkers in tumor infiltrate and in peripheral blood.
- Explore ^{18}FDG-PET as a biomarker of response
- Explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open label, multicenter, Phase 1 study that will be conducted in 2 parts: a dose escalation part and a cohort expansion part. The objective of the dose escalation part is to assess the safety and tolerability and determine the MTD and/or RP2D of E7046. In the cohort expansion part an additional 6 to 16 subjects will be treated at the RP2D to further characterize safety, efficacy, PK, and PD. E7046 is a novel cancer immune therapy and as this is the first study in humans therefore a cautious approach in the first cohort of subjects is prudent. Staggered start of dosing in the first cohort will thus be implemented to ensure exposure of a limited number of subjects in the initial dosing cohort.

The applicability of conventional *MTD finding* Phase 1 designs for compounds with minimum expected toxicity has been discussed in various publications, and several alternative strategies have been advised (Rubinstein and Simon, 2003). Pharmacokinetics based and minimal biologically active dose finding designs rely not only on having robust estimates from preclinical data but also the use of biological correlative response endpoints that might get complicated by issues of assay adequacy and access to biological tissues. Another strategy for Phase 1 studies of targeted compounds is to compare dose levels with regard to biological response in normal tissue using an optimized highly reproducible assay. If use of normal tissue for assessing biological response is not possible or if a highly reproducible assay is not available, characterisation f of an optimal biologic dose may not be feasible or might require a large sample size.

The study design was selected taking these concerns into account. A major consideration was that the toxicities of E7046 are likely to be moderate in the dose range planned and an MTD may not be reached (according to preclinical results). It is anticipated that the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, collected from all dose levels tested. Accordingly, a modification of the standard 3+3 design was selected, where dose cohorts of 6 subjects will be enrolled at each of the 4 dose levels to be tested so as to provide sufficient data for selecting RP2D in the absence of an MTD.

9.1.1 Dose Escalation

9.1.1.1 Dose Escalation Design

E7046 will be tested in sequential escalating dose cohorts of 6 subjects per cohort, at the dose levels shown in Table 1. Subjects will be assigned to a dose level in the order of study entry. Intermediate dose levels may be explored.

Table 1 Dose Cohorts in E7046 Dose-Escalation

Dose level	No. of Subjects	E7046 Dose
-1	6	75 mg QD
1	6	125 mg QD
2	6	250 mg QD
3	6	500 mg QD
4	6	750 mg QD

QD = once daily.

The schema for dose escalation is adopted and modified from the traditional 3+3 design and is shown in Figure 3. Dose limiting toxicities are defined in Section 9.1.1.2.

Enrollment for first dose cohort (125 mg QD): (see Figure 3 Panel B)

In the first cohort, staggered dosing will be employed as described below.

Suspected severe immune reactions (ssIR) are defined as listed in the CTCAE v4,03 "Immune System Disorders", including Allergic Reaction, Anaphylaxis, and Cytokine Release Syndrome.

First 3 subjects (Subjects 1, 2, and 3)

- Initially one subject (Subject #1) will be enrolled and dosed.
  - If after 14 days of dosing no suspected severe immune reactions are observed, another 2 subjects (Subjects # 2 and 3) will be enrolled and dosed.
  - If within the first 14 days, Subject #1 experiences a suspected severe immune reaction, another subject (Subject #2) will be enrolled and dosed.
    - If after 14 days of dosing no suspected severe immune reactions are observed for Subject #2, another subject (Subject #3) will be enrolled and dosed.
    - If within the first 14 days, Subject #2 also experiences a suspected severe immune reaction, enrollment in this dose cohort will stop. A lower dose level of 75 mg QD (Dose Level -1) may be tested. Enrollment of the 6 subjects at Dose Level -1 will follow the same staggered schema as described for Dose Level 1.

Next 3 subjects (Subjects 4, 5, and 6)

- After evaluation of the first 3 subjects for DLTs after 21 days (Cycle 1), enrollment will continue as follows:
  - If ≤1 of 3 first subjects experiences DLTs in Cycle 1, the remaining 3 subjects (Subjects # 4, 5, and 6) in the first cohort will be enrolled and treated.
  - If >1 of 3 first subjects experiences DLTs in Cycle 1, a lower dose level of 75 mg (dose level -1) will be tested, following the same enrollment schema as described for Dose Level 1.

Enrollment of subsequent dose cohorts:

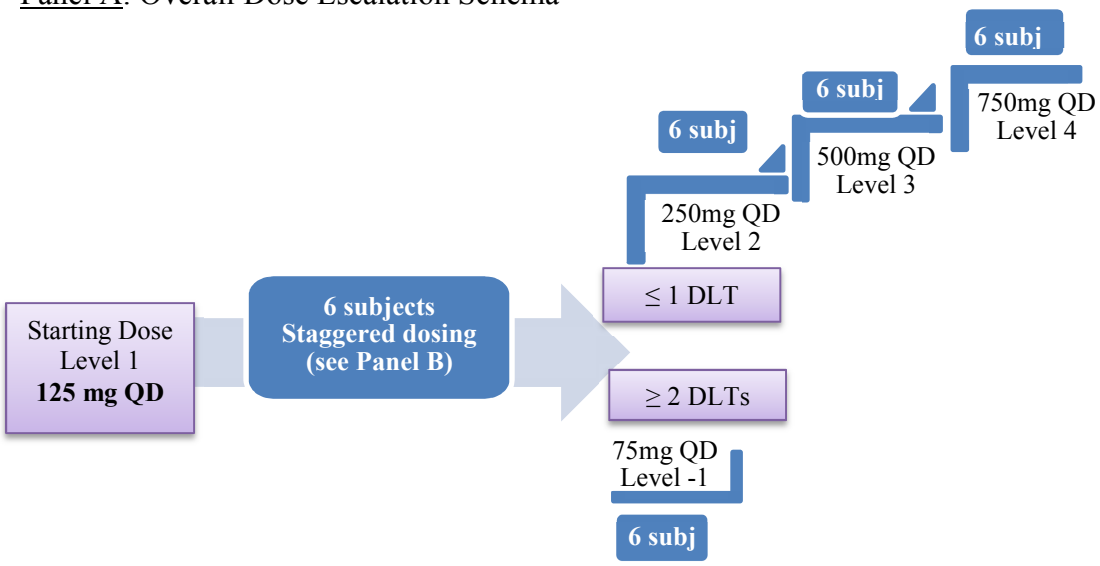
- There will be no staggered dosing after the first dose cohort, however the subject enrolment will be controlled so that no more than one subject will be dosed on the same day.
- If ≥2 of 6 subjects in any dose cohort experiences a DLT, then dose escalation will be stopped.
- If ≤1 of 6 subjects in a dose cohort experiences a DLT, then 6 subjects will be enrolled at the next higher dose level. Dose escalation will continue until a dose level is reached where ≥2 subjects experience a DLT, or when 750 mg is reached based on

an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested.

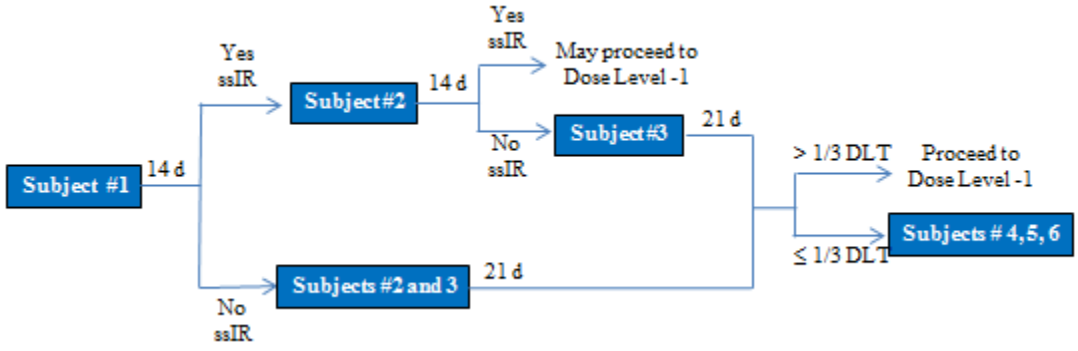
Additional enrollment (if necessary)

If needed for selection of RP2D, an additional 3 subjects may be enrolled at 1 or 2 selected dose levels.

Panel A: Overall Dose Escalation Schema



Panel B: First Dose Cohort (Staggered dosing)



ssIR = suspected severe immune reaction

Figure 3 Schema for Dose Escalation

9.1.1.2 Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) are any of the following drug related toxicities (any toxicities considered related, probably related, or possibly related to E7046) occurring during Cycle 1 as judged by the investigator.

- Nonhematologic toxicity ≥ Grade 3 (except diarrhea, nausea and vomiting unless lasting >3 days despite optimal supportive care)
- Confirmed (with a second measurement after 24 hours) nonhematologic appropriately-graded laboratory findings of Grade ≥3 that were ≤ Grade 1 at baseline
- Hematologic toxicity:
  - Grade 4 neutropenia for ≥ 5 days, or Grade 3 neutropenia with fever (fever is 38.4 ºC),
  - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or lasting >7 days
- Any other toxicity assessed as related to E7046 treatment, and which in the opinion of the study investigator(s) and the sponsor physician constitutes a dose-limiting toxicity
- Subjects who have missed ≥ 7 days of dosing in Cycle 1 due to drug-related toxicity (but not qualifying for a DLT) will be assessed as experiencing a DLT.

Grading of toxicities is based on National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 (Appendix 4).

Adverse events occurring after Cycle 1 may be considered DLTs upon discussion between the investigator(s) and the sponsor physician.

The following toxicities will not be considered DLTs:

- Grade ≤3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade ≤3 immune-related adverse event (irAE) that resolves to Grade 1 or less within 7 days, while not constituting a DLT for dose escalation purposes, may preclude further administration of study drug or study drug may be continued at a reduced dose after discussion and agreement with Eisai medical monitor.
  - An irAE, a subset ofAEs, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Subjects who for reasons other than drug related toxicity or a DLT, fail to complete 75% of the planned total dose in Cycle 1, (equivalent to 16 out of 21 days) will be replaced.

Assessment of DLTs will be discussed and agreed to by investigator(s) and sponsor physician prior to proceeding to the next dose level, and the decision will be documented.

9.1.1.3 Maximum Tolerated Dose

The MTD is defined as one dose level below the dose level where ≥2 of 6 subjects experience a DLT. If ≤1 of 6 subjects in all dose cohorts experience a DLT, then an MTD has not been reached.

9.1.1.4 Selection of the Recommended Phase 2 Dose

The RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, for all dose levels tested. The investigator and sponsor will jointly evaluate the data and select the RP2D.

Selection of the RP2D will take place after the last subject in the Dose Escalation part completes the Treatment Phase (Section 9.1.3.2).

The RP2D will be the selected according to the following guidelines:

1. The RP2D will not exceed the MTD.
2. Toxicities other than DLTs will be considered, including: AEs assessed as related to study drug treatment but not considered dose-limiting, the nature and frequency of toxicities, and the emergence of any specific category of toxicities.
3. Evidence of clinical activity, as available.
4. Available pharmacodynamic data.
5. Consideration will be given to select RP2D dose that will sustain E7046 exposure above IC_{50} or IC_{90} values for EP4 inhibition for the duration of dosing period.

If two or more potential RP2D dose levels cannot be distinguished using the criteria above, cohort expansion (see below) may take place at up to 2 dose levels to obtain data for up to 6 additional subjects per dose level. Selection of RP2D will be based on this larger dataset.

If serious related toxicities are observed in later cycles beyond Cycle 1 a reduction of the MTD and/or RP2D may be considered. This determination will be made by the investigators and the sponsor physician, taking into account all available data.

9.1.2 Cohort Expansion

An expansion cohort of 6 to 16 subjects will be enrolled and treated at the RP2D after completion of the dose escalation part. The objective is to further evaluate safety and efficacy of E7046 at the RP2D and further characterize PK and PD. Subjects will be selected from the same tumor types as in the dose escalation part.

9.1.3 Study Phases

The study will consist of three phases for each subject: Pretreatment Phase, Treatment Phase, and Extension Phase.

A schematic of the 3 Phases is shown in Figure 4.

PHASE	**Pretreatment** →		**Treatment** →			**Extension** →			
PERIOD	Screening	Baseline	Treatment Cycle 1			Treatment Continuation (Cycle 2 and beyond)		EOT	Follow -Up
Day	–28 to –1	-3 to -1	D1	D8	D15	D1	D8 (C2-6 only)		
VISIT	1	2	3	4	5	6, 8 etc	7, 9 etc	98	99

EOT = End of Treatment

Figure 4 Study Design

9.1.3.1 Pretreatment Phase

The Pretreatment Phase is 28 days before the first day of dosing, and consists of:

- A **Screening Period** spanning Day -28 to Day -1, to obtain informed consent, assess disease characteristics at study entry, and to establish protocol eligibility
- A **Baseline Period**, which consists of the last 3 days of the Screening period (Day -3 to Day -1), to establish baseline characteristics and confirm eligibility to start treatment.

9.1.3.2 Treatment Phase

Treatment Phase is Cycle 1 (Day 1 - 21) where evaluable subjects will be assessed for DLT.

At the end of the Treatment Phase subjects continue to the Extension Phase.

9.1.3.3 Extension Phase

The Extension Phase consists of 2 periods:

- **Treatment Continuation Period**, during which subjects will continue in Cycle 2 and beyond to receive the same treatment they received during the Treatment Phase.

  The **Treatment Continuation** period will start at the end of the Treatment Phase and will end with the completion of the Off-Treatment Visit (which will occur within 30 days after the last administration of the study drug). It consists of study drug treatment on a 21-day cycle, regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in Schedule of Procedures (Section 9.5.6.1) . Subjects will discontinue the study drug and become Off-Treatment at the time of disease progression, development of unacceptable toxicity, withdrawal of consent or termination of the study program.

- A **Follow-Up Period**, for study assessments after discontinuation from study treatment.

  The Follow-up Period will begin the day after the Off-Treatment Visit and will continue as long as the study subject is alive until the completion of the primary analysis, unless the subject withdraws consent or until the sponsor terminates the study. Subjects, who discontinue study treatment without disease progression will continue to be followed and undergo tumor assessments every 6 weeks until disease progression or until the start of another anticancer treatment. In the follow-up period, subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1week) for survival, performance status and subsequent anticancer treatments. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

9.2 Discussion of Study Design

This is an open label, multicenter, Phase 1 study that will be conducted in 2 parts: a dose escalation part and a cohort expansion part.

E7046 will be administered as a single agent orally once daily (QD) continuously in 21-day cycles. Animal PK studies have shown that a once daily schedule administered continuously is likely to be adequate to maintain systemic concentrations of E7046 in an efficacious range, at the doses planned (Section 7.1.3.2).

E7046 will be tested in sequential escalating dose cohorts of 6 subjects per cohort, to identify a MTD and/or a RP2D (Section 9.1 for detailed discussion of the rationale for this design). Preclinical studies suggest that toxicities are anticipated to be moderate in the dose range planned to be studied, and that an MTD may not be reached. In this case, the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, for all dose levels tested. Dose cohorts of 6 subjects each will be enrolled at each of the 4 dose levels to be tested, rather than employing a traditional 3+3 design. This number of subjects per cohort is expected to provide sufficient data for selecting a RP2D in the absence of an MTD.

The starting dose of 125 mg (first-in-human dose) is the human equivalent dose of 1/9 the minimally toxic dose in preclinical species. Based on preclinical PK/PD data, this dose was also projected to be in the efficacious range based on sustaining exposure at IC_{50} – IC_{90} of EP_4 inhibition in vitro and on effectiveness in animal tumor models. The maximum dose of 750 mg is >5 fold the starting dose of 125 mg, the latter being an anticipated efficacious dose. The maximum dose is also limited by the number of capsules to be ingested (6 capsules, with current capsule strength) being close to the maximum feasible number of capsules that could be taken at a time.

This study will enroll subjects with tumor types that are characterized by high levels of myeloid infiltrate. The expected action of E7046 is to inhibit immunosuppressive cells of myeloid lineage. Preclinical work showed that E7046 had antitumor activity in six syngeneic tumor models with significant intratumoral monocytic cell infiltration, but not in other two tumor models with minimal monocytic cell infiltration. Thus, this selected population is considered appropriate for the expected mechanism of action of E7046.

9.3 Selection of Study Population

Approximately 30 to 40 subjects in total will be enrolled: 24 in the Dose Escalation part and 6 to 16 in the expansion cohort. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Age ≥18 years.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
3. Life expectancy ≥12 weeks.
4. Subjects must have any of the following tumor types, confirmed by available pathology records or current biopsy, that is advanced, nonresectable, or recurrent and progressing since last antitumor therapy, and for which no alternative standard therapy exists:
   pancreatic adenocarcinoma, renal clear cell carcinoma, SCCHN, NSCLC, colorectal cancer (CRC), hepatocellular carcinoma (HCC), ovarian serous epithelial cancer, bladder transitional cancer, cervical cancer and triple-negative breast cancer
5. Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) must have been completed at least 4 weeks before study drug administration, and all AEs have either returned to baseline or stabilized.
6. Prior definitive radiation therapy must have been completed at least 6 weeks before study drug administration and the irradiated lesions should show evidence of progression if they are intended to be considered target lesions. Prior palliative radiotherapy must be completed at least 2 weeks before study drug administration. The radiotherapy related side effects must have resolved before the study entry. No radiopharmaceuticals (strontium, samarium) will be allowed within 8 weeks before study drug administration.
7. Subjects must have accessible tumors and consent to repeated biopsy for performance of correlative tissue studies.
8. Must have at least one measurable lesion per irRECIST (Appendix 1):
   a. At least 1 lesion of ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node that is serially measurable according to irRECIST using computerized tomography/magnetic resonance imaging (CT/MRI).
   b. Lesions that have had definitive external beam radiotherapy or locoregional therapies such as radiofrequency (RF) ablation or brachytherapy must show evidence of progressive disease to be deemed a target lesion.
9. Prior treated brain or meningeal metastases must be without evidence of progression (confirmed by MRI) for at least 8 weeks and off immunosuppressive doses of systemic

steroids (>10 mg/day prednisone or equivalent) for at least 4 weeks before study drug administration.

10. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >7.5 to 10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks before study drug administration.
11. Subjects with prior Hepatitis B or C are eligible on the condition that subjects have adequate liver function as defined by Inclusion Criterion #16 and Exclusion Criterion #5.
12. Left ventricular ejection fraction (LVEF) >50% on echocardiography or multiple gated acquisition (MUGA) scan.
13. Adequate renal function defined as serum creatinine <1.5 × ULN (or use SI units or calculated creatinine clearance ≥50 mL/min per the Cockcroft and Gault formula [Appendix 3]).
14. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥1500/mm^3 (≥ 1.5 × 10^3/µl)
    b. Platelets ≥100,000/mm^3 (≥ 100 × 10^9/L)
    c. Hemoglobin ≥9.0 g/dL
15. Adequate liver function:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
    b. Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (≤5 × ULN if subject has liver metastases). If alkaline phosphatase is >3 × ULN (in absence of liver metastases) or >5 × ULN (in presence of liver metastases) AND the subject also is known to have bone metastases, the liver-specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of total alkaline phosphatase
16. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5.
17. Willing and able to comply with all aspects of the protocol.
18. Provide written informed consent prior to any study-specific screening procedures.
19. Females must not be lactating or pregnant at screening or baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrheic, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential must not have had unprotected sexual intercourse within 30 days prior to study entry and must agree to use a highly effective method of contraception, from the last menstrual period

prior to initiation of treatment, during Treatment Cycles, and for 30 days after the final dose of study treatment, and have a male partner who uses a condom. Highly effective contraception includes:

a. Double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.
b. Placement of an intrauterine device.
c. Established hormonal contraceptive methods: oral, injectable, or implant. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

Female subjects exempt from this requirement are subjects who practice total abstinence or have a male partner who is vasectomized with confirmed azoospermia. If currently abstinent, the subject must agree to use a double barrier method as described above if they become sexually active during the Treatment Cycles, and for 30 days after study drug discontinuation

20. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception and use a condom throughout the study period and for 90 days after study drug discontinuation).

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast that has completed curative therapy.
2. Subjects with any active autoimmune disease (Appendix 2) or a documented history of autoimmune disease, poorly controlled asthma or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy. Subjects with asthma who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study**.**
3. Subjects with inflammatory bowel disease.
4. Known human immunodeficiency virus (HIV) infection.
5. Active infection requiring therapy, including known positive tests for Hepatitis B surface antigen and hepatitis C virus (HCV) RNA.
6. Major surgery within 4 weeks before the first dose of study drug.
7. Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids except inhaled or intranasal corticosteroids (with minimal systemic absorption).

8. Inability to take oral medication, or malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of E7046.
9. Any other major illness that, in the investigator's judgment, will substantially increase the risk associated with the subject's participation in this study.
10. Use of other investigational drugs within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
11. Prior exposure to drugs that are antagonists of colony stimulating factor-1 receptor (CSF1R) like but not limited to emactuzumab (RG7155) (Roche), PLX3397 (Plexicon), JNJ40346627 (J & J)**.**
12. Use of any live vaccines (eg, intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines) within 28 days.
13. Prolongation of corrected QT (QTcF) interval to >480 msec when electrolytes balance is normal.
14. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac arrhythmia requiring medical treatment (including oral anticoagulation).
15. Females who are pregnant (positive urine test) or breastfeeding.
16. Any history of a medical condition or a concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.

9.4 Treatments

9.4.1 Treatments Administered

E7046 will be administered as a single agent orally once daily (QD) continuously in 21-day cycles. Subjects will be required to fast 2 h before and 2 h after the E7046 dose. The daily dose should be taken at about the same time. Refer to Table 1 for doses to be administered.

E7046 is supplied as capsules in strengths of 75 mg and 125 mg. Additional capsule strengths may be made available during the study. Drug will be supplied by the sponsor in labeled containers.

9.4.1.1 Dose modifications

Toxicity will be managed by concomitant medication (as appropriate), treatment interruption, dose reduction and treatment discontinuation, or a combination of these.

Dose reduction is allowed for all subjects during all cycles of treatment.

Subjects who experience a DLT in Cycle 1 may be allowed to continue study drug at a reduced dose after discussion with sponsor Medical monitor if this is judged to be in their best interest (see dose modification guidelines below).

Guidelines for dose adjustments

During E7046 treatment, dose interruptions and reductions due to toxicity will be implemented according to the instructions presented in Table 2. Any dosage interruptions of more than 3 days should be discussed with sponsor's medical monitor to establish if longer dose interruption is needed.

Table 2 E7046 Dose Reduction and Interruption Instructions

E7046-related Toxicity[a]	During Therapy	Approximate dose adjustment[b]
Grade 1		
All occurrences	Continue E7046 treatment	Maintain dose level
Grade 2		
1st occurrence	Interrupt E7046 until resolved to Grade ≤1 or baseline[c]	Maintain dose level
2nd occurrence (same toxicity)		Reduce by one dose level of starting dose
3rd occurrence (same toxicity)		Reduce by two dose levels of starting dose
4th occurrence (same toxicity)		Discuss with Sponsor
Grade 3		
1st occurrence	Interrupt E7046 until resolved to Grade ≤1 or baseline[c]	Reduce by one dose level of starting dose
2nd occurrence (same toxicity)		Reduce by two dose levels of starting dose
3rd occurrence (same toxicity)	Discontinue E7046 treatment	Not applicable
Grade 4: Discontinue E7046[d]		

a. Excluding alopecia and nausea, vomiting or diarrhea not receiving adequate treatment.

b. Subjects assigned to dose level -1 (75 mg) will not be dose-reduced and will not continue treatment under the conditions in which dose reduction is mandated. Subjects assigned to dose level 1 (125 mg) can only be dose-reduced by one dose level and will not continue treatment under the conditions in which reduction of two dose levels is mandated.

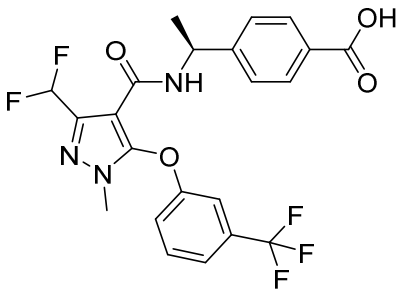
c. A delay of E7046 for more than 7 days due to any treatment-related toxicity must be discussed with the sponsor before treatment can be resumed.

d. Exclude Grade 4 hematologic toxicity of less than 72 hours duration.

9.4.2 Identity of Investigational Product

9.4.2.1 Chemical Name, Structural Formula of E7046

- Test drug code: E7046
- Generic name: N/A
- Chemical name: 4-{(1*S*)-1-[({3-(Difluoromethyl)-1-methyl-5-[3-(trifluoromethyl)phenoxy]-1*H*-pyrazol-4-yl}carbonyl)amino]ethyl}benzoic acid
- Molecular formula: $C_{22}H_{18}F_5N_3O_4$
- Molecular weight: 483.40
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E7046 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

See Sections 9.1.1 and 9.1.2.

9.4.4 Selection of Doses in the Study

See Section 9.3.

9.4.5 Selection and Timing of Dose for Each Subject

See Section 9.3.

9.4.6 Blinding

This is an open label study; the treatment will not be blinded.

9.4.7 Prior and Concomitant Therapy

The following are prohibited:

- Drugs interfering with platelet aggregation, including NSAIDs and anticoagulant s including LMWH, warfarin, anti-Xa agents
    - Physiological replacement of corticosteroid dosing representing physiological doses up to 7.5 mg/day will be allowed
- Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs): Subjects on these hypertensives at study entry should be switched to other hypertensives prior to study drug dosing
- Other antitumor therapies such as chemotherapy, palliative radiotherapy, antitumor interventions (surgical resection, thoracocentesis, etc.), or antitumor immunotherapy.
- Other investigational drugs

9.4.8 Prohibitions and Restrictions During the Study Period

9.4.8.1 Food

Subjects are to fast 2 hours before and 2 hours after taking study medication.

On days when subjects will have ^{18}FDG-PET/CT scans performed, they will refrain from eating (water intake is encouraged to maintain adequate hydration) for approximately 6 hours (specific instructions will be provided by the imaging core laboratory, including recommendations for morning and afternoon appointments, and for diabetic subjects) before injection of the radiotracer prior to scanning (ACR, 2006).

9.4.8.2 Physical Activity Restrictions

To minimize uptake of radiotracer into muscle, the subject should avoid strenuous exercise or exposure to cold before undergoing a ^{18}FDG-PET/CT examination for a minimum period of at least 6 hours but a target of 24 hours prior to the examination. Specific instructions will be provided by the imaging core laboratory.

9.4.9 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form (FDA 1572), where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license (required in the US) or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drug (dispensing, inventory, and record keeping) following the sponsor's instructions (if necessary, "Instructions for Handling of Investigational Products and Trial-Related Materials") and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drug to be used other than as directed by this protocol. Study drug will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drug, dispensing of study drug to the subject, collection and reconciliation of unused study drug that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drug to the sponsor or (where applicable) destruction of reconciled study drug at the site. This includes, but may not be limited to: (a) documentation of receipt of study drug, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drug and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drug and empty and partially empty containers from used study drug are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drug and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drug to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drug that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drug may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Demography, Disease History, and Other Baseline Assessments

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

Medical history, concomitant medications, physical examination, echocardiogram/MUGA, 12-lead ECG, pregnancy test, vital signs, hematology, blood chemistry, urinalysis, surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history must be noted in the medical history and current medical conditions Case Report Form (CRF). ECOG will be assessed.

Information on history of current malignancy will be collected, including tumor type and prior therapy, with response and duration of response for each therapy.

For tumor biopsy assessment,please refer to Section 9.5.4.3.

9.5.2 Efficacy Assessments

Tumor assessments will be performed by investigators based on both irRECIST and modified RECIST 1.1 at each assessment time point. **However, the treatment decisions by the Investigator will be based on irRECIST.** The Sponsor may request that images acquired for tumor assessments be sent to an imaging core laboratory for archival and potential independent analysis. Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (during the 6th week; counting from C1D1) during treatment cycles in both the Treatment Phase and the Extension Phase. Screening Week 6 and Week 12 scans (unless the imaging core laboratory determines that the Screening ^{18}FDG-PET scans do not have a FDG-PET-evaluable lesion) must be performed on a PET/CT scanner that is capable of acquiring diagnostic quality CT scans. CT scans (with oral and/or intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), using the above tumor assessment schedule, and as indicated clinically. Skin lesions may only be considered as non-index lesions (no photographs required) or as new lesions if they meet the minimum size criteria for a measurable lesion. Subjects with SCCHN must also have head and neck scans performed. Chest disease may not be followed using chest x-ray. The same method of assessment must be used at all time points as used at Screening.

For subjects with TNBC or NSCLC, bone scans will be performed at the Screening Visit, every 24 weeks, or sooner if clinically indicated, and at confirmation of complete response (irCR). Lesions identified on bone scans must be verified with correlative cross-sectional imaging.

A brain scan (CT with contrast or MRI with and without gadolinium chelate) must be performed at Screening to assess potential CNS disease and/or metastases. For subjects with

previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed within one week to confirm a irCR in conjunction with the CT scans for response confirmation, or if clinically indicated.

The first radiological assessment of tumor response status will be performed at Week 6, unless there is clinical indication warranting earlier radiologic imaging. If imaging at 6 weeks shows immune-related stable disease (irSD), treatment will be continued and the next imaging studies will be conducted at Week 12. Responses (immune-related partial response [irPR] or irCR) should be confirmed no less than 4 weeks following the initial response (generally at the next q6 weeks [every-6-weeks] scheduled tumor assessment visit).

If the tumor assessment is immune-related progressive disease (irPD), treatment should continue and tumor assessments repeated at least 4 weeks later, but generally at the next scheduled tumor assessment time point in order to confirm irPD. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating irPD, treatment may be continued. If repeat imaging confirms irPD, subjects will be discontinued from study therapy. In determining the tumor timepoint response, investigators should consider all target lesions as well as non-target lesions and new lesions.

The decision to continue study treatment after the first evidence of irPD is at the investigator's discretion based on the clinical status of the subject as described in Table 3 below.

Subjects may receive study treatment while waiting for confirmation of irPD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If PD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact Sponsor to discuss continuing treatment.

Table 3 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Subsequent scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Subsequent scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or is clinically stable per investigator's discretion

CR = complete response, N/A = not applicable, PD = progressive disease, PR = partial response.

Subjects going off study without disease progression will also undergo tumor assessments every 6 weeks until disease progression is documented or another anticancer therapy is initiated.

irRECIST guidelines are described in Appendix 1.

Tumor assessments per modified RECIST 1.1 will follow Eisenhauer et al. (2009), however, up to 10 target lesions, up to 5 per organ, may be selected (as opposed to a maximum of 5 target lesions, up to 2 per organ).

9.5.3 Pharmacokinetic Assessments

Blood samples for PK analyses will be collected during Cycle 1 on Day 1 and Day 8 at predose (0 h), 0.5, 1, 2, 4, 6, 8, and 10 and 24h postdose.

Urine samples for PK analyses will be collected during the Dose Escalation part only during Cycle 1.

Plasma and urine concentrations of E7046 will be measured by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. The major metabolite identified in nonclinical species (M1) will also be analysed.

Instructions on PK sample collection, handling, storage, and shipment of samples will be detailed in the study-specified Laboratory Manual to be provided to the site.

9.5.4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.4.1 Overview of Biomarker Approach

Pharmacodynamics (PD) biomarkers including Proof of Mechanism (POM) biomarkers to show target engagement and Proof of Principle (POP) biomarkers to show impact of E7046 treatment on disease will be evaluated from collected samples.

Proof of Mechanism may be demonstrated by an alteration in expression of EP_4 response genes and/or proteins, as EP_4 is the molecular target of E7046.

POP for E7046 could be a change in intratumoral immune cell populations consistent with inhibition of EP_4 signaling such as a decrease in the ratio of M2/Total TAM or an increase in the number of CD8+ T cells. POP could also be a decrease in the number or ratio of MDSC in circulation.

Retrospective testing for potential subject stratification (PS) markers will also be explored.

Results from biomarker studies will be used to aid the selection of dose and for correlation with drug efficacy. The biomarker assessments planned for this study are summarized in Table 4. Details, including methodology and analyses, are described below.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Table 4 Biomarker assessments

Biomarker sample	Time points	Analyses	Potential Utility
Plasma protein	Predose C1D1, 24hr after first dose, C1D8, C1D15	TAM/MDSC-related cytokines, eg, PGE_2,)	POM
Blood mRNA	Predose C1D1, 24hr after first dose, C1D8, C1D15	Immune Gene expression	POM
Paired tumor biopsy	Predose and during Cycle 2	T cell and macrophage infiltration	POP
Archived tumor	Screening	To be decided	
Whole blood	Baseline, predose C1D1, C1D8, C1D15, C2D1, C3D1, C5D1	Circulating MDSC	POP, POM, PS
Blood plasma	Baseline, time points for at each CT tumor assessment, and End of Treatment	Cell-free nucleic acid	
Blood genomic DNA	Baseline	Pharmacogenomic analysis	PG
Urine	Cycle 1 Day 1 pre-dose (0-hr) and Cycle 1 Day 1 and Day 8 post-dose to 6hr, 6 to-12hr, 12 to 24hr.	PGE_2 metabolite	POM

C1D1 = Cycle 1 Day 1, MDSC = myeloid-derived suppressor cell, PG = prostaglandin, PGE = prostaglandin e2, POM = Proof of Mechanism, POP = Proof of Principle, PS = subject stratification, TAM = tumor-associated macrophages).

9.5.4.2 Protein and mRNA markers in serum

Blood samples will be collected for plasma protein biomarker analysis at the time points indicated in Table 6. Samples will be analyzed for PGE_2 and other immune cell related markers (eg, cytokines) using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods and new technology.

Blood samples will also be collected for RNA analysis. Gene expression testing including but not limited to EP_4 will be performed and correlated with PK, safety, or PD data.

9.5.4.3 Intratumoral immune cell populations

The following intratumoral changes reflect the immunological effects of E7046 that would constitute POP, and will be analyzed in paired tumor biopsy samples collected before and after E7046 treatment:

- Decrease in the ratio of M2/total TAM
- Increase in number of cytotoxic T cells (CD8+)

Quantitation of these cell populations will be by image analysis after IHC detection using immune cell infiltration markers (including but not limited to CD163, CD68, CD8) as well as markers for general tumor/stromal architecture.

Paired tumor core needle biopsies will be obtained according to institutional standard operating procedures, with appropriate subject consent. Subjects should have the biopsy before administration of the first dose of E7046 and at any time during Cycle 2 or later, as long as the subject has had uninterrupted treatment at least 5 days prior to biopsy.

In the event that a subject is clinically required to have further tumor biopsy while on study, FFPE tissue from the procedure should be obtained for shipment to Eisai or a designated central laboratory for exploratory biomarker analysis.

These biomarker assessments will provide information on intratumoral tissue target inhibition, relevant PD biomarkers and potential markers of response.

9.5.4.4 Archival Tumor

Archived, fixed tumor tissue will be collected (if available). These tissues may be used for assessment of mutations and other genetic alterations or immune cell infiltration status and its associated molecules that may be important in the development and progression of cancer.

9.5.4.5 Circulating immune cell population

Myeloid-derived suppressor cell levels are anticipated to be affected by E7046 treatment as the generation of this cell population is EP_4-dependent. Changes in MDSC in blood in response to E7046 treatment will be evaluated as a potential Proof of Principle biomarker.

MDSC levels at baseline will also be evaluated for any correlation with efficacy or safety outcomes.

Blood samples will be collected for measuring circulating MDSC. The time points are selected to explore both early (within days) and more delayed (weeks) effects of E7046 treatment. MDSC will be quantitated by flow cytometry.

These assessments evaluating response-related and safety-related outcomes as well as being for potential use in diagnostic development are exploratory. When new research results emerge, the parameters and methods for the PD biomarker analysis may change.

9.5.4.6 Blood plasma cell-free nucleic acid analysis

A blood plasma sample will be collected for potential cell-free nucleic acid analysis. Nucleic acid isolated from blood plasma samples may be used to explore tumor genetic alterations, including mutations observed in archival tumor samples and mutations that may emerge with drug treatment.

9.5.4.7 Pharmacogenomic analysis

A blood sample will be collected for pharmacogenomics (PG) analysis. The role of DNA sequence variability on the absorption, distribution, metabolism, and elimination (ADME) of (insert study drug) may be evaluated in this study. Variation in E7046 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or pharmacodynamic (PD) data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor.

9.5.4.8 Urine biomarker analysis

Urine for biomarker analyses will be collected from the unspun urine collected for urinalysis. These samples will be used to explore urine protein, genetic changes, and drug metabolite.

PGE-M is a stable major metabolite for PGE-2. Urinary PGE-M can be used to quantify systemic PGE-2 production and serve as biomarker for disease progression and drug response.

9.5.4.9 General

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to E7046 or cancer and for potential diagnostic development.

Archived tumor tissue samples and blood samples for PD, PG, and other biomarker assessments will be collected from all consented study subjects, except where prohibited by regional or local laws.

Samples may be used for biomarker discovery or validation to identify blood or tumor biomarkers that may be useful to predict treatment response (efficacy, PD), PK, and safety-related outcomes. Samples may also be used for potential diagnostic development. In addition, biomarkers identified in other clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis will be based on the clinical outcome of the study, the signals observed in other clinical studies, and/or the scientific rationale of the study.

9.5.4.10 Exploratory Imaging Biomarkers

Before each ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)/CT (FDG-PET/CT) examination, subjects will have a fasting serum glucose sample drawn and analyzed before injection of the ^{18}FDG radiotracer. Serum glucose must be ≤120 mg/dL for nondiabetic or ≤200 mg/dL for diabetic subjects or the scan must be postponed or rescheduled. The FDG-PET/CT scans will be performed using the guidelines provided by the Imaging Core Laboratory designated by the sponsor. It is particularly critical that subjects are imaged within 1 hour ±10 minutes after injection of the radiotracer.

An FDG-PET/CT scan will be performed within 7 days before Cycle 1 Day 1. FDG-PET/CT scans will be sent to the Imaging Core Lab for assessment of evaluability. Subjects whose pretreatment scans show evidence of FDG avid tumor lesion(s) and are considered PET evaluable will have a second FDG-PET/CT scan performed coincident with the Week 6 tumor assessments and a third scan coincident with the Week 12 tumor assessments. FDG-PET/CT time points may be changed based on emergent data. All FDG-PET/CT scans will be quantitatively evaluated by the imaging core lab for imaging biomarkers of metabolic activity in select lymphoid tissue and malignant lesions, and tumor volume as specified in the Image Review Charter.

NOTE: Changes in standardized uptake value (SUV) should NOT be used to assess tumor response or progressive disease. ^{18}FDG-PET assessment is for exploratory purposes only.

9.5.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/MUGA scans, electrocardiograms (ECGs), and physical examinations as detailed in Table 6. The effects of E7046 on cardiovascular repolarization will be evaluated via continuous Holter/ECG monitoring. Subjects with decreasing hemoglobin levels or gastrointestinal symptoms indicative of gastrointestinal bleed should be evaluated for a potential gastrointestinal bleeding source as appropriate.

9.5.5.1 Adverse Events and Events Associated with Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7046.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE.)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious AEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Subjects with onset of an AE or deterioration of a preexisting AE will be followed until resolution to baseline status, start of a new anticancer treatment, or death.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03 (Appendix 4). Investigators will report all CTCAE grades for AEs.

The criteria for assessing severity are different than those used for seriousness (Section 9.5.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.5.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires in subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria: gastrointestinal bleeding, colitis, irAE, Grade >2 diarrhea.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations due to disease progression
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for PK analysis should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.5.3 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) Coagulation panel* : Activated partial thromboplastin time (aPTT), thrombin time, PT, INR, fibrinogen
Chemistry	
Electrolytes	Chloride, potassium, sodium, calcium, phosphorus
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen (UREA/BUN), creatinine
Other	Albumin, cholesterol, HDL, LDL triglycerides, lactate dehydrogenase, , total protein, uric acid. fasting glucose will be done at baseline and after that in conjuction with FDG-PET as per Table 6, or if urine dipstick examination finds glucose or ketones
Urinalysis (dipstick)	Glucose, ketones, protein, and blood. Microscopic examination (if blood or protein is abnormal in dipstick analysis)

RBC = red blood cell, WBC = white blood cell.

*Coagulation panel: baseline, weekly in cycle 1 and then once every cycle thereafter

Clinical laboratory tests will be performed by site local laboratories. Laboratory certification as available will be included in the final clinical study report for this study.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (Section 9.5.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), height, and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 6) by a validated method. Blood pressure and pulse will be measured after the subject has been supine for 5 minutes. All BP measurements should be performed on the same arm using the same cuff size and the same equipment.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize

the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.5.5 Physical Examinations

Comprehensive and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Abbreviated Physical Examination

Health status will be assessed by brief evaluation of the chest (including heart and lungs), abdomen and limbs, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.5.6 Electrocardiograms

Twelve-lead electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 6).

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 9.5.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

Twelve-lead ECGs will be extracted from the same timepoints as for PK blood draws during the first 12 hous after dose on Day 1 and Day 8. Potential effects of E7046 on ECG parameters (heart rate, PR, QRS and QTcF) will be analyzed as change from predose baseline, by timepoint and for the QTcF interval, using exposure response analysis.

9.5.5.7 Echocardiograms or Multiple Gated Acquisition Scans

Echocardiograms or MUGA scans will be obtained as designated on the Schedule of Procedures/Assessments (Section 9.5.6.1, Table 6). A MUGA scan (using technetium-99m-pertechnetate) or an echocardiogram to assess LVEF will be performed during the Pretreatment Phase (within 21 days before Cycle 1 Day 1), if clinically indicated, and during the Off-Treatment Visit (window of ±1 week). MUGA scans and echocardiograms will be performed locally in accordance with the institution's standard practice. Whichever modality

is used for an individual subject at screening should be repeated for all subsequent LVEF assessments for that subject.

9.5.5.8 Pregnancy Test

A serum β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments (Table 6).

9.5.6 Schedule of Procedures/Assessments

9.5.6.1 Schedule of Procedures/Assessments

Table 6 presents the schedule of procedures/assessments for the study.

Table 6 Schedule of Procedures / Assessments in Study E7046-G000-101

	Phase	Pretreatment[a]		Treatment			Extension			
	Period	Screening	Baseline	Cycle 1			Treatment Continuation[b] (Cycle 2 and beyond)		Off-Treatment[c]	Follow-up[c]
	Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
	Day	-28 to -1	-3 to -1	1	8	15	1	8 (C2-6 only)		
CRF	**Procedures/Assessments**									
S	Informed consent	X								
S	Inclusion/exclusion criteria	X								
S	Medical history	X								
S	Physical examination[d] and Vital signs[e]	X	X	X	X	X	X		X	
N	Echocardiogram / MUGA[f]	X							X	
S	Pregnancy test[g]	X	X	X					X	
S	ECOG performance status	X	X	X			X		X	
S	12-lead ECGs[h]	X	X	X			X		X	
S	ECG Holter monitoring[i]			X	X					
S	Hematology / Blood chemistry[j]	X	X	X	X	X	X	X	X	
S	Urinalysis[k]	X		X	X	X	X	X	X	
N	Genomic DNA[l]		X							
S	PK and PD urine collection[m]			X	X					
S	PK blood samples[n]			X	X					
N	PD blood samples[o]		X[o]	X	X[o]	X[o]	X[o]		X[o]	
N	Paired tumor biopsy and archived tumor[p]	X					X[p]			
N	^{18}FDG PET/CT[q]		X				X[q]			
S	Tumor assessments: CT or MRI[r]	X		Every 6 weeks or sooner if clinically indicated						
S	CT or MRI of the brain[s]	X		X						
N	Bone Scan[t]	X		Every 24 wks, or sooner if clinically indicated, and at confirmation of irCR						
S	E7046 administration[u]			Continuous daily dosing						
S	Adverse Events[v]	X	X	X					X	
S	Prior and concomitant medications[v]	X	X	X					X	
S	Survival status[w]									X

For CRF: S = standard assessment, N = nonstandard assessment (study-specific), N/A = not applicable.

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, C1D1 = Cycle 1 Day 1, CR = complete response, CRF = case report form, CT = computed tomography, CTCs = circulating tumor cells, DNA = deoxyribonucleic acid, ECG = electrocardiograms, ECOG = Eastern Cooperative Oncology Group, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, h = hour, HR = heart rate, irPR = immune-related partial response, irRECIST = immune-related RECIST, IV = intravenous, MDSC = myeloid-derived suppressor cell(s), MRI = magnetic resonance imaging, myeloid-derived suppressor cell, MUGA = multiple gated acquisition, PD = pharmacodynamic, PGE2 = prostaglandin e2, PK = pharmacokinetic, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SCCHN = squamous cell carcinoma of head and neck, SAE = serious adverse event, TNBC = triple-negative breast cancer.

a. The Screening Period extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. The baseline assessments may be performed from Day -3 to Day -1 (before the first dose of E7046). Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication.

b. The off-treatment assessment should occur within 30 days after the final dose of study treatment. Subjects who discontinue study for reasons other than disease progression will be followed until disease progression or death. All anticancer therapies will be collected (the sponsor may choose to stop the collection of therapies after the first anticancer treatment.

c. Visit windows are allowed from Cycle 3 onwards as follows: Day 1 (±3 days), and Day 8 (±3 days). There must be at least 5 days between the Day 1 and Day 8 visit for any given treatment cycle.

d. A comprehensive physical examination will be performed at the Screening Visit and at the Off-Treatment Visit. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated.

e. Vital signs include BP, HR, RR, and body temperature, as well as weight and height. BP, HR, and RR will be collected after the subject has been sitting for 5 minutes. Height will be measured at the Screening Visit only.

f. MUGA scans or echocardiograms will be performed at Screening, during the Off-Treatment Visit (window of ±1 week), and if clinically indicated. MUGA scans and echocardiograms will be performed locally in accordance with the institution's standard practice.

g. A serum pregnancy test (β-hCG) will be performed at screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine pregnancy test will be performed at baseline before the first E7046 dose, Cycle 1 Day 1and at the Off Treatment visit.

h. 12-Lead ECGs will be collected at the following time points: Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after study drug administration); and at the Off-Treatment Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

i. Continuous Holter/ECGs (12-h/12-lead) to be collected during Cycle 1 on Day 1 and Day 8 at predose (3 timepoints within 45 minutes), and 0.5, 1, 2, 4, 6, 8, and 10 h postdose. At each of these timepoints, subjects should be supinely resting for at least 10 minutes prior to and 5 minutes after the nominal time and the time points when the subject is supinely resting should be recorded. When coinciding, blood draws, vital signs and 12-lead safety ECGs should be performed immediately after the timewindow for ECG extraction.

j. Hematology and blood chemistry samples will be obtained before drug administration. Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication. Before drug administration on Cycle 1, Days 1 and 8, a complete blood count should be drawn. Coagulation panel: baseline, weekly in cycle 1 and then once every cycle thereafter. See Table 5 for list of tests.

k. Urine samples will be obtained before drug administration (either formal urinalysis or urine dipstick for protein and glucose are acceptable).

l. Genomic DNA samples will be collected at baseline. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

m. All urine excreted will be collected as follows: Cycle 1 Day 1 pre-dose (0-hr) and Cycle 1 Day 1 and Day 8 post-dose to 6hr, 6 to-12hr, 12 to 24hr. Total urine volume collected in each time interval will be recorded. Urine will be analyzed for PK (E7046, M1 metabolite) and PD (PGE-M, metabolite of PGE2).

n. Blood samples for PK analyses will be collected during Cycle 1 on Day 1 and Day 8 at predose (0 h), 0.5, 1, 2, 4, 6, 8, and 10 and 24h postdose.

o. Blood samples for PD mRNA and protein biomarker analysis (one PAX gene tube and one lavender top EDTA tube) will be collected at the following time points: predose

(0 h) on Cycle 1 Day 1, 24 h after first dose, Day 8, and Day 15. Blood for cell free nucleic acid will be collected at C1D1 predose, at each tumor assessment, and at the end of treatment. Blood for MDSC in circulation will be collected at baseline, C1D1 predose, C1D8, C1D15, C2D1, C3D1, and C5D1.

p. Paired tumor biopsies will be obtained, with appropriate subject consent. Subjects will have the biopsy before the first dose of E7046 and during Cycle 2, as long as the subject has had uninterrupted treatment at least 5 days prior to biopsy. In addition, archived fixed tumor tissue will be collected if available (instructions to be provided in a separate manual).

q. ^{18}FDG PET/CT scans should be performed according to instructions provided by the imaging core lab and sent to the core lab for quantitative assessments. Scans should be performed at baseline (within 7 days before C1D1) for all subejcts, repeat scans in conjunction with the Week 6 and Week 12 tumor assessments timepoints only for subjects with evidence of evaluable FDG avid tumor lesion(s) at screening. ^{18}FDG-PET/CT scan timepoints may be changed based on emergent data.
Subjects must have a fasting serum glucose assessment performed before injection of the PET tracer for each scan. FDG-PET/CT will not be performed if serum glucose is >120 mg/dl for nondiabetics or >200 mg/dl for diabetic subjects.

r. Tumor assessments will be performed based on irRECIST and modified RECIST1.1. Treatment decisions will be based on irRECIST. Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (during the 6th week; counting from C1D1) during treatment cycles in both the Treatment Phase and the Extension Phase. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/ Day 1), using the above tumor assessment schedule, and as indicated clinically. Skin lesions may only be considered as non-index lesions (no photographs required) or as new lesions to add to the tumor burden sum. Subjects with SCCHN must also have head and neck scans performed at all tumor assessment timepoints.

   MRI scans may be used instead of CT scans for (head, neck) abdomen and pelvis; however, chest must be assessed using CT. Chest disease may not be followed using chest x-ray. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast. The same method of assessment must be used at all time points as used at Screenin**g.**

s. Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast within 4 weeks prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a irCR. For subjects with history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability

t. A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF) to assess bone metastases will be performed within 6 weeks prior to C1D1 and then every 24 weeks (within that 24th week) from C1D1 for tumor types known to metastasize to bone (eg TNBC, NSCLC, RCC.), or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate irCR has been achieved, a bone scan will be required at confirmation of irCR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. If a non-target lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based upon the other non-target lesions and will not be considered not evaluable (NE).

u. E7046 should be taken daily at the dose assigned, with fasting 2 hours before and 2 hours after ingestion of E7046 capsules. On visit days, subjects should not take study medication before evaluations are performed.

v. Adverse events and prior and concomitant medications information to be collected at every study visit.

w. Subjects who discontinue study will be followed for survival. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Follow up on subsequent treatment and clinical response will be collected.

9.5.6.2 Description of Procedures/Assessments Schedule

Please refer to the footnotes in the table of the Schedule of Assessments.

9.5.7 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in oncology studies.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.8 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.8.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 30 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.8.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (Section 9.5.8.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study. A subject who becomes pregnant may remain in the study if the investigator judges that the potential benefit to the subject outweighs any potential risk to the subject or the fetus and the subject gives informed consent for the further participation.

9.5.8.3 Reporting of Events Association with Special Situations

9.5.8.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Section 9.5.8.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.8.4 Expedited Reporting

The sponsor must inform investigators (or, as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.8.5 Breaking the Blind

Not applicable.

9.5.8.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.9 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 6).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.10 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

Descriptive statistics will be used for continuous variables using n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum, unless otherwise specified. Categorical variables will be summarized as number (percent) of subjects.

9.7.1 Statistical and Analytical Plans

For purposes of the final analysis, data cutoff will occur when the last enrolled subject completes 6 cycles of treatment (ie all subjects have been followed by a minimum of 6 cycles) or subjects discontinue early, whichever occurs first. The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

Primary Endpoints (Dose Escalation part):

- Safety/tolerability profile of E7046.
- MTD and/or the RP2D.

Secondary Efficacy endpoints:

- Objective response rate

  The ORR is the proportion of subjects achieving a best overall response of confirmed partial or complete response (irPR + irCR), according to irRECIST (Appendix 1) from first dose date until disease progression/recurrence. Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate.

- Duration of response

  Duration of response is defined as the time from the date of first documented confirmed irCR/irPR until the first documentation of confirmed disease progression or death, whichever comes first.

- Progression-free survival

  Progressive-free survival is defined as the time from first dose date to the date of the first documentation of confirmed disease progression or death (whichever occurs first) using irRECIST. The censoring rule for events will be defined in the SAP.

- Disease control rate

  The DCR is the proportion of subjects achieving irPR + irCR + irSD from first dose date until disease progression/recurrence.

- Clinical benefit rate

  The CBR is the proportion of subjects achieving irPR + irCR + irSD [lasting at least 24 weeks] from first dose date until disease progression/recurrence.

Exploratory endpoints:

- ORR, DCR, CBR, PFS according to modified RECIST 1.1
- Effect of E7046 on tumor ^{18}FDG uptake and volume will be explored as potential early response biomarkers. Variables will include total tumor volume of target lesions, metabolic tumor volume (SUV >2.5), maximum SUV of a single pixel, metabolic peak of a 1 cm spot, and summed SUVs of target lesions. Summary statistics and change from baseline will be presented.
- Effect of E7046 on ^{18}FDG uptake by spleen and/or draining lymph nodes will be explored as a potential biomarker of immune activation. Variables will include total volume and metabolic volume of spleen and, where possible, draining lymph nodes, Summary statistics and change from baseline will be presented.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set will include all subjects who received at least one dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics. This analysis set will also constitute the **Safety Analysis Set**.

DLT Evaluable Set will consist of those subjects who are evaluable for the DLTs (Section 9.1.1.2). This will be the analysis set for DLT analysis.

Pharmacokinetic (PK) Analysis Set will include all subjects who have received at least one dose of study drug and have at least one evaluable plasma concentration.

9.7.1.3 Subject Disposition

The number (percentage) of randomized and treated subjects will be summarized as well as subjects who completed the study/discontinued from the study and reasons for discontinuation by treatment group. The number (percentage) of subjects who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized by treatment cohort.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized and listed for each treatment cohort. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as N, mean, standard deviation, median, Q1, Q3, minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms (verbatim terms) for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. A listing of prior and concomitant medications will be included in the clinical study report for this protocol.

9.7.1.6 Dose Escalation Primary Endpoints Analyses

Safety/tolerability profile of E7046 will be assessed. The incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters will be summarized, by dose levels.

Maximum tolerated dose. The incidence of DLTs by dose level will be tabulated. The MTD will be determined per protocol definition.

RP2D. The RP2D will be selected as described in Section 9.1.1.4.

9.7.1.7 Efficacy Analyses

The ORR , response duration, time to response, PFS, DCR, and CBR will be listed and descriptively summarized as appropriate.

- Response duration and time to response: Summary statistics (median Q1, Q3, and range) for will be summarized on subjects achieving a best overall response of confirmed partial or complete response (irPR + irCR). The time to response will be censored at the last tumor assessment for subjects who leave the study before a response, death or progression is observed.
- PFS: Subjects who discontinue from the study for reasons other than progression of disease will be treated as right-censored observations at the time of the last response evaluation (subjects who withdraw from the study due to progressive disease will be considered to have a disease progression between the last visit and the time of withdrawal). PFS (by irRECIST) will be reported in both summary tables and Kaplan–Meier curve.

9.7.1.8 Pharmacokinetic Analyses

Plasma and urine concentrations of E7046 and its major metabolite M1 will be tabulated and summarized by dose level, day, and time. PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: maximum drug concentration (C_{max}), time to reach maximum concentration following drug administration (t_{max}), area under the concentration × time curve (AUC); and if data permit, elimination half-life ($t_{½}$), total body clearance (CL), volume of distribution (Vd), renal clearance (CLr), accumulation ratio (R), and fraction excreted (fe).

9.7.1.9 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacodynamic, PG and other biomarker analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

9.7.1.10 Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety data to be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and the results of physical examinations.

Safety assessments will consist of monitoring and recording all AEs and SAEs, using CTCAE version 4.03; regular laboratory evaluation for hematology, blood chemistry, and urine values; and regular performance of physical examinations, periodic measurement of vital signs, ECGs, and MUGA scans at baseline and as clinically indicated.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

The effects of E7046 on cardiovascular repolarization will be evaluated via 12-hour, 12-lead continuous Holter/ECG monitoring during Cycle 1 Day 1 and Day 8 in the Dose Escalation part of the study only. Individual ECGs will be extracted in replicate from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for QTc using Fridericia's (QTcF) correction factors. The primary QTc parameter will be QTcF. Secondary parameters (heart rate, PR and QRS) and T wave morphology will be evaluated. Potential effects of E7046 will be evaluated as change-from predose baseline heart rate, PR, QRS and QTcF by post-dosing timepoint. For purposes of QT assessment, exposure response analysis will be performed of the relationship between E7046 plasma levels and ΔQTcF.

Safety ECGs will be analyzed using descriptive statistics for ECG parameters and changes from baseline will be presented by treatment cohort abnormal readings will be identified as those outside (above or below) the reference range. ECG findings will be summarized.

9.7.1.10.1 Extent of Exposure

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation due to AEs will be summarized.

9.7.1.10.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 18.0 or higher) lower level term (LLT) closest to the verbatim term. Adverse events will be presented by MedDRA preferred term (PT) nested within primary system organ class (SOC).

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline), or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment cohort. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).and by relationship to study drug (Yes [related] and No [not related]), respectively.

9.7.1.10.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of will be summarized by visit and treatment cohort using descriptive statistics. Qualitative parameters listed in Section 9.5.5.3 and change from baseline values will be summarized using frequencies (number and percentage of subjects).

9.7.1.10.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiratory rate, temperature, weight and changes from baseline will be presented by day and time after dosing and treatment cohort.

MUGA Scans: MUGA scans and/or echocardiograms will be assessed locally to determine LVEF. Summary statistics (standard deviation, median, and range) for LVEF changes from baseline will be calculated and summarized.

9.7.2 Determination of Sample Size

The sample size of 30 to 40 subjects is considered adequate for the purposes of selecting a dose.

The expected sample size for the dose escalation part of this trial will be up to 24 subjects. Per the dose escalation design adopted and modified from the traditional 3+3 design (Section 9.1.1.1), there will be a maximum of 4 planned cohorts and there will be 6 subjects each cohort to allow for adequate assessment of tolerability, clinical benefit, PK, PD data and integrated evaluation of safety so as to select RP2D. Additional 6 to 16 subjects will be enrolled in the expansion cohort to confirm RP2D.

The dose escalation part and the extension part yield a total maximum sample size of 40 subjects.

9.7.3 Interim Analysis

No interim analyses are planned.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

Baum V, Bühler P, Gierschner D, Herchenbach D, Fiala GJ, Schamel WW, et al. Antitumor activities of PSMA×CD3 diabodies by redirected T-cell lysis of prostate cancer cells. Immunotherapy. 2013;5(1):27-38.

Brahmer JR, Tykodi SS, Chow QM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med. 2012;366:2455-2465.

Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Ganjoo KN, Witten D, Patel M, Espinosa I, La T, Tibshirani R, et al. The prognostic value of tumor-associated macrophages in leiomyosarcoma: a single institution study. Am J Clin Oncol. 2011;34(1):82-6.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.

Heusinkveld M, van der Burg SH. Identification and manuipulation of tumor associated macrophages in human cancers. J Transl Med. 2011;9:216.

Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E, et al. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med. 2014; 6:237ra67.

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; ;363(8):711-23.

Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nat Rev Cancer. 2009;9(4):239-52.

Medrek C, Pontén F, Jirström K, Leandersson, K. The presence of tumor associated macrophages in tumor stroma as a prognostic marker for breast cancer patients. BMC Cancer. 2012.;12:306.

Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell, 2010;141:39-51.

Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014; ;384(9948):1109-17.

Rubinstein LV, Simon RM . Phase I clinical trial design. In: Budman DR, Calvert AH, Rowinsky EK (editors). Handbook of anticancer drug development. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 297-308.

Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565-70.

The American College of Radiology (ACR). Uniform protocols for Imaging in Clinical Trials. Philadelphia, PA: ACR; 2006.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15(23):7412-20.

Zhang QW, Liu L, Gong CY, Shi HS, Zeng YH, Wang XZ, et al. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. PLoS One. 2012;7(12):e50946.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2

years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor (this can be amended depending on the protocol). Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1: Adaptation of RECIST for evaluation of immune therapy activity in solid tumors: Immune-Related Response Evaluation Criteria in Solid Tumors (irRECIST)

Investigators should follow the guidelines provided here which are an adaptation of RECIST 1.1 and immume-related response criteria (irRC). The following guide represents a summary of irRECIST and is meant to help investigators in providing more objective and reproducible immune therapy related tumor response assessments in solid tumors.

The key changes for irRECIST are:

- In contrast to RECIST 1.1, irRECIST allows the site to select up to ten (10) target lesions at baseline, five (5) per organ, if clinically relevant via CT/MRI scans. Skin lesions are not permitted for selection as target lesions for this study.
- The ability to continue treatment, if clinically stable, until repeat imaging scans ≥ 4 weeks later (in most cases at the next scanning timepoint 6 weeks later) to confirm Progressive Disease (irPD)

irRECIST Lexicon	
1. Baseline Assessments	
Measurable (Target) lesions	Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis (SDi) for nodal lesions • Identify up to 10 lesions, not more than 5 from one organ system. Lymph nodes are considered one organ system • Likely to be reproducible across all timepoints • Representative of tumor burden • May include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation • Sum of diameters (SOD) of all target lesions including nodal and non-nodal are reported as baseline SOD which is used for assessing tumor response at follow-up timepoints
Bone lesions	Regardless of the imaging modality, blastic bone lesions will **not be** selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.
Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the SOD of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
Lesions with Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progression in the lesion.
Nonmeasurable (Non-Target) lesions	Non-target lesions will include: • Measurable lesions not selected as target lesions. There is no limit to the number of non-target lesions that can be recorded at baseline • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc. • Multiple non-target lesions from the same organ may be captured as a single item on the eCRF (e.g. multiple liver metastases) Non-target lesions should be reported as present at baseline
SOD $_{\text{baseline}}$	Sum of diameters at baseline = LDi of all non-nodal + SDi of all nodal target lesions

2. Time Point Assessments After Baseline	
Target lesion measurements	Locate image that optimizes the LDi of the non-nodal target lesion or short axis of target node(s). There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate timepoint SOD (SOD $_{timepoint}$). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5mm should be entered on eCRF. • If target lesion is between 5-10mm, actual diameter should be entered on eCRF • If target lesion splits into 2 or more lesion then the LDi of split lesions will be added and entered in place of that lesion • If two target lesion merged to form one lesion than LDi of one should be entered as '0mm' while the other lesion should have the diameter of the merged lesion
Non-Target Lesion Assessment	Non-target lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of non-target lesions primarily contributes to the overall response assessments of irCR. Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even in the presence of stable disease or a partial response in the target lesion is indicative of irPD. irCR is not possible unless all non-target lesions are absent.
Definition of New lesion	Any lesion which was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment must be used by the PI • May include a lesion in an anatomical location that was not scanned at baseline (i.e. brain) • Should be unequivocal and not due to differences in scanning technique • If equivocal, should be assessed at next timepoint; if present, PD is the date the lesion was first seen (not the date confirmed)
3. irRECIST Overall Tumor Assessment	
irCR	• Complete disappearance of all measurable and nonmeasurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed irCR). • Lymph nodes must decrease to < 10 mm in short axis. • Confirmation of response is required ≥ 4 weeks later, preferably at next timepoint, to be considered a confirmed irCR.
irPR	• If the **$SOD_{timepoint}$ of TLs decreases by ≥ 30 % compared to $SOD_{baseline}$** and there are no unequivocal new lesions, and no progression of non-target disease, it is an irPR (unconfirmed). • Confirmation is required ≥ 4 weeks later, preferably at next timepoint, to be considered a confirmed irPR.

<table>
<tr><td>irSD</td><td>Failure to meet criteria for irCR or irPR in the absence of irPD.
If the sum of the TLs and the status of the non-target lesions do not reach the criteria to meet irPR or irPD (increase ≥20% and at least 5 mm absolute increase in SOD compared to nadir†) the response is irSD.
irSD = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir.
†SOD_{nadir}: Lowest measure SOD of TLs at any timepoint from baseline onward.</td></tr>
<tr><td>irPD</td><td>Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or irPD for non-target lesion(s) or unequivocal new lesion(s).
Confirmation of progression is recommended at a minimum of 4 weeks after the first irPD assessment (preferably at next tumor assessment timepoint).
The decision to continue study treatment after the first evidence of PD is at the Investigator’s discretion based on the clinical status of the subject as described in table below.
<table>
<tr><td></td><td colspan="2">Clinically Stable</td><td colspan="2">Clinically Unstable</td></tr>
<tr><td></td><td>Imaging</td><td>Treatment</td><td>Imaging</td><td>Treatment</td></tr>
<tr><td>1st radiologic evidence of PD</td><td>Repeat imaging at ≥ 4 weeks (next TA timepoint) to confirm PD</td><td>May continue study treatment at the Investigator’s discretion while awaiting confirmatory scans</td><td>Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only</td><td>Discontinue treatment</td></tr>
<tr><td>Subsequent scan confirms PD</td><td>No additional imaging required</td><td>Discontinue treatment</td><td>No additional imaging required</td><td>N/A</td></tr>
<tr><td>Subsequent scan shows SD, PR or CR</td><td>Continue regularly scheduled imaging assessments</td><td>Continue study treatment at the Investigator’s discretion</td><td>Continue regularly scheduled imaging assessments</td><td>May restart study treatment if condition has improved and/or clinically stable per Investigator’s discretion</td></tr>
</table>
Subjects may continue receiving study treatment while waiting for confirmation of irPD if they are clinically stable as defined by the following criteria:
Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
No decline in ECOG performance status
Absence of rapid progression of disease
Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention</td></tr>
</table>

	If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact Sponsor to discuss continuing treatment
irNE	Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure

Derivation of irRECIST overall responses

Measurable response	**Nonmeasureable response**		
Target Lesions (% change in SOD)*	**Non-Target Lesions Status**	**New Lesions Status**	**Overall Response (irRECIST)**
↓100	Absent	Absent	irCR[¥]
↓100	Present/NE	Absent	irPR[¥]
↓≥30	Present/Absent/NE	Absent	irPR[¥]
↓<30 to <20↑	Present/Absent/NE	Absent	irSD
↓100 ↓≥30 ↓<30 to <20↑ NE	Present/Absent/NE	Present	irPD[¥]
↓100 ↓≥30 ↓<30 to <20↑ NE	Unequivocal progression	Any	irPD[¥]
↑≥20 from nadir	Any	Any	irPD[¥]
NE	Present/Absent/NE	Absent	irNE[¥]

* Decreases assessed relative to baseline, including measureable lesions only.

[¥] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Appendix 2: Pre-Existing Autoimmune Diseases

Diseases that may be autoimmune related include but are not limited to the following:

- Acute disseminated encephalomyelitis
- Addison's disease
- Alopecia universalis
- Ankylosing spondylitis
- Antiphospholipid antibody syndrome
- Aplastic anemia
- Asthma
- Autoimmune hemolytic anemia
- Autoimmune hepatitis
- Autoimmune hypoparathyroidism
- Autoimmune hypophysitis
- Autoimmune myocarditis
- Autoimmune oophoritis
- Autoimmune orchitis
- Autoimmune thrombocytopenic purpura
- Behcet's disease
- Bullous pemphigold
- Celiac disease
- Chronic fatigue syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Chung-Strauss syndrome
- Crohn's disease
- Dermatomyositis
- Diabetes mellitus type 1
- Dysautonomia
- Eczema
- Epidermolysis bullosa acquista
- Gestational pemphigoid
- Giant cell arteritis
- Goodpasture's syndrome
- Graves' disease
- Guillain-Barré syndrome
- Hashimoto's disease
- IgA nephropathy
- Inflammatory bowel disease
- Interstitial cystitis
- Kawasaki's disease
- Lambert-Eaton myasthenia syndrome
- Lupus erythematosus
- Lyme disease - chronic
- Meniere's syndrome
- Mooren's ulcer
- Morphea
- Multiple sclerosis
- Myasthenia gravis
- Neuromyotonia
- Opsoclonus myoclonus syndrome
- Optic neuritis
- Ord's thyroiditis
- Pemphigus
- Pernicious anemia
- Polyarteritis nodusa
- Polyarthritis
- Polyglandular autoimmune syndrome
- Primary biliary cirrhosis
- Psoriasis
- Reiter's syndrome
- Rheumatoid arthritis
- Sarcoidosis
- Scleroderma
- Sjögren's syndrome
- Stiff-Person syndrome
- Takayasu's arteritis
- Ulcerative colitis
- Vitiligo
- Vogt-Kovanagi-Harada disease
- Vulvodynia
- Wegener's granulomatosis

This list is from the study protocol provided as part of the publicationTopalian 2012.

Appendix 3: Cockcroft–Gault Calculation of Creatinine Clearance

Subjects must have adequate renal function as evidenced by serum creatinine ≤1.8 mg/dL or calculated creatinine clearance ≥50 mL/min per the Cockcroft–Gault formula as defined below.

Cockcroft–Gault Calculation for Creatinine Clearance

Male	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine } (\mu\text{mol/L})} = \text{XX mL/min}$
Female	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{serum creatinine } (\mu\text{mol/L})} = \text{XX mL/min}$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Appendix 4: Common Terminology Criteria for Adverse Events (v4.03)

The National Cancer Institute's *Common Terminology Criteria for Adverse Events* (CTCAE v4.03 published 28 May 2009; v4.03: June 14, 2010) provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 4.03 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v4.03 grading refers to the severity of the AE. CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Common Terminology Criteria for Adverse Events v4.03 Grading

Grade	Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Source: Cancer Therapy Evaluation Program, NCI. CTCAE v4.03. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

For further details regarding MedDRA, refer to the MedDRA website: http://www.meddramsso.com.

CTCAE v4.03 is available online: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7046-G000-101

Study Protocol Title: An Open-Label Multicenter Phase 1 Study of E7046 in Subjects With Selected Advanced Malignancies

Investigational Product Name: E7046

IND Number: 125272

EudraCT Number: 2014-004823-37

SIGNATURES

Authors:

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18 Aug 2016
Date

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Eisai, Inc.

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18-AUG-2016
Date

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INVESTIGATOR SIGNATURE PAGE

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I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator | Signature | Date