1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	MORAb-009-201
Study Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination with Pemetrexed and Cisplatin in Subjects with Unresectable Malignant Pleural Mesothelioma
Sponsor:	Morphotek, Inc. 210 Welsh Pool Road Exton, PA 19341 US Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	MORAb-009 (amatuximab)
Indication:	Malignant pleural mesothelioma
Phase:	2
Approval Date:	v1.0 11 Dec 2014 (original protocol) v2.0 24 Apr 2015 (Amendment 01) v3.0 30 Jan 2017 (Amendment 02)
IND Number:	12894
EudraCT Number:	2014-004489-85
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 Morphotek, Inc. (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.

REVISION HISTORY

Revisions to Version 3.0 (per Amendment 02)

Date: 30 Jan 2017

Change	Rationale	Affected Protocol Sections
A business decision was made to discontinue further enrollment in the study and significantly amend the protocol to discontinue all ongoing study procedures and conduct, but provide a mechanism for patients already randomized to the amatuximab (MORAb-009) arm to continue to receive ongoing study treatment until discontinuation for disease progression or tolerability issues. Per the amendment, only core information necessary for safety monitoring and reporting will be collected. No efficacy data will be reported. Subjects who were randomized to placebo and all subjects in follow-up have been discontinued from the study.	Significant delays in initiating the program, which led to a significant shift in the timing of the primary and final analyses. As a result, the original rationale for the study is now compromised by the introduction of newer treatment regimens (eg, bevacizumab) and the rapid clinical development of several investigational agents (eg, immune checkpoint inhibitors), such that the program no longer aligns with the developing standard of care. No new safety or efficacy data were generated during the conduct of this trial to date to inform this business decision.	Throughout

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: Amatuximab (MORAb-009)
Name of Active Ingredient: amatuximab
Study Protocol Title A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination with Pemetrexed and Cisplatin in Subjects with Unresectable Malignant Pleural Mesothelioma
Investigators List of investigators to be maintained separately by the sponsor
Sites List of investigational sites to be maintained separately by the sponsor
Study Period and Phase of Development Phase 2
Objectives The primary objective of this amendment is to provide ongoing amatuximab treatment access consistent with the primary 009-201 treatment schedule to those trial subjects randomized to the amatuximab arm who, at the discretion of their investigator, may obtain ongoing clinical benefit. The secondary objective of this amendment is to monitor safety of ongoing subjects through the collection of serious adverse event information.

Study Design

The primary 009-201 study was designed as a multicenter, double-blind, randomized, parallel-group study, using a placebo control or amatuximab 5 mg/kg, administered weekly, designed to evaluate the safety and efficacy of amatuximab in combination with pemetrexed and cisplatin in subjects with unresectable MPM who have not received prior systemic therapy. Subjects were randomized in a 1:1 ratio using interactive response technology (IRT). Subjects were stratified by Performance Status (ECOG 0 or 1).

Subjects who qualified were randomized and entered the Combination Treatment Phase to receive Test Article (amatuximab or placebo) on Day 1 of each week, and chemotherapy (pemetrexed and cisplatin) on Day 1 of each 21-day cycle, for 6 cycles of treatment. Following completion of the Combination Treatment Phase (ie, after a subject has received at least 4 cycles of Combination Treatment), subjects who had not progressed entered the Maintenance Treatment Phase where they continued to receive the Test Article on a weekly basis until disease progression. All subjects were to be followed for survival (ie, Follow-up Phase).

An Independent Data Monitoring Committee (IDMC) performed safety assessments as determined by the committee up until the time of this amendment. No new safety concerns were noted.

Eisai made a business decision to discontinue any further enrollment in the study as of 11Jan2017 and to significantly amend the trial protocol. Per this amendment:

- Subjects who were randomized to amatuximab and are still on active treatment may consent to continue to receive weekly treatment with amatuximab until disease progression or intolerable toxicity at the discretion of the principal investigator (PI).
- Subjects randomized to placebo or who were in follow-up have been discontinued from the study.
- Clinical management and ongoing assessments of subjects will continue per standard of care as determined by the PI.
- Only serious adverse event (SAE) and subject discontinuation data will be collected by the Sponsor.
- Subjects will not be followed for efficacy.

Number of Subjects

At the time enrollment was closed, 108 subjects were randomized. The study has been unblinded and 27 total subjects randomized to amatuximab would be eligible to remain in the study for continued treatment based on investigator discretion and the subject consent.

Inclusion Criteria

All subjects were enrolled in the study under the inclusion criteria outlined in the previous protocol amendment dated 24 Apr 2015. The following criteria apply to this amendment:

1. Subjects who were enrolled in the study and randomized to the amatuximab treatment arm may, at the discretion of the PI, consent to continue to receive amatuximab therapy until disease progression, intolerable toxicity, or withdraw of consent.
2. Subjects of childbearing potential must be surgically sterile or consent to use a highly effective method of contraception throughout the study period. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, 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). If

a patient of childbearing potential is neither surgically sterile nor postmenopausal, highly effective contraceptive measures must start either prior to or at Screening and continue throughout the entire study period and for at least 6 months after the last dose of chemotherapy and at least 30 days after the last dose of amatuximab is administered (whichever is later). A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Periodic abstinence, the rhythm method, the withdrawal method, condoms, and diaphragms are not acceptable methods of contraception. Women of childbearing potential must also refrain from egg cell donation for 6 months after the final dose of investigational product.

3. 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 throughout the study period and for 6 months after discontinuation of chemotherapy and for 5 weeks after amatuximab discontinuation [whichever is later]). No sperm donation is allowed during the study period and for 90 days after amatuximab discontinuation.

Exclusion Criteria

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

1. Subjects previously randomized to placebo
2. Subjects who have not signed the updated informed consent form associated with this amendment
3. Subjects who have radiographic or clinical disease progression or intolerable toxicity such that ongoing amatuximab treatment through this study is not appropriate

Study Treatments

Amatuximab 5 mg/kg by intravenous (IV) infusion once weekly. In addition, subjects receive pemetrexed 500 mg/m^2 followed by cisplatin 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 6 cycles during the Combination Treatment Phase.

Duration of Treatment

The maximum duration of participation for individual subjects continuing treatment is expected to be approximately 6-12 months. Subjects will no longer be followed for efficacy. Continuing subjects may discontinue for intolerable toxicity of the study drugs, disease progression, or may withdraw consent for any other reason at any time without prejudice.

Concomitant Drug/Therapy

In order to prevent hypersensitivity AEs, subjects must be premedicated approximately 30 to 60 minutes prior to each infusion of amatuximab with acetaminophen 650 mg by mouth and diphenhydramine 25 mg to 50 mg by mouth or IV, or the local equivalents. Subjects will also receive prophylactic treatment for pemetrexed with folic acid, vitamin B12, and dexamethasone at each cycle of Combination Treatment according to the investigational site's standard practice.

Assessments

Efficacy Assessments:

No formal analysis of efficacy will be performed.

Safety Assessments:

Per this amendment, subjects will continue to receive physical exams, clinical laboratory tests and other medical assessments at the discretion of the PI per standard of care practice. Data from these assessments, including any AEs, will be documented in the subject's medical records but no longer be collected by the Sponsor with the exception of SAEs and treatment discontinuation information. SAE reporting must still meet standard expedited reporting requirements as outlined in this amendment.

Pharmacokinetic Assessments:

Samples collected to date may be analyzed. Per this amendment no additional samples will be collected.

Pharmacodynamic Assessments:

Not applicable

Pharmacogenomic Assessments:

Samples collected to date may be stored and analyzed per the terms of the original informed consent form signed by each subject. Per this amendment no additional samples will be collected.

Biomarker Assessments:

Samples collected to date may be stored and analyzed per the terms of the original informed consent form signed by each subject. Per this amendment no additional samples will be collected.

Bioanalytical Methods

Serum Amatuximab Assay:

Samples collected to date may be analyzed as previously described and results will be summarized in a final report. Per this amendment no additional samples will be collected.

Amatuximab ADA Analysis:

Samples collected to date may be stored and analyzed per the terms of the original informed consent form signed by each subject. Per this amendment no additional samples will be collected.

Biomarker Analyses:

Samples collected to date may be stored and analyzed per the terms of the original informed consent form signed by each subject. Per this amendment, no additional samples will be collected.

Statistical Methods

No formal efficacy analyses are planned. All data collected prior to database lock including safety data will be summarized and listed as appropriate in an abbreviated final study report.

Interim Analysis

An interim analysis for futility will not be performed.

Sample Size

At the time enrollment was stopped 108 subjects were randomized. Twenty-seven subjects randomized to amatuximab were eligible to remain in the study for continued treatment based on investigator discretion and the subject consent.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AEI	adverse event of interest
ASCO	American Society of Clinical Oncology
β-hCG	beta-human chorionic gonadotropin
BSA	body surface area
CA	Competent Authority
CA125	cancer antigen 125
CFR	Code of Federal Regulations
C_{min}	minimum observed concentration
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CT	computed tomography
DCR	disease control rate
DHAE	drug hypersensitivity adverse event
DPSM	duration of performance status maintenance
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPI	glycosylphosphatidylinositol
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG1/κ	immunoglobulin G subtype 1-kappa
Investigational product	amatuximab (MORAb-009)
IRB	Institutional Review Board

Abbreviation	Term
IV	intravenous
IRT	Interactive Response Technology
LCSS-Meso	Lung Cancer Symptom Scale for mesothelioma
MedDRA	Medical Dictionary for Regulatory Activities
MORAb-009	amatuximab, the monoclonal antibody to be tested in this protocol
MPM	malignant pleural mesothelioma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal antiinflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PI	principal investigator
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
QOL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
SPECT	single photon emission-computerized tomography
SUSAR	suspected unexpected serious adverse response
TEAE	treatment-emergent adverse event
TMF	Trial Master File
TRAE	treatment-related adverse event
US	United States

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 International Conference on Harmonisation (ICH) E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Federal Regulations, Title 21 CFR Part 56, for United States [US] studies). 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[s] [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documentation of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any Test Article 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 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 of any reportable adverse events (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 time of data cutoff for the final analysis. It is estimated that the study will end in December, 2017.

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 of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)

- 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 US 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
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse responses (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 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 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, an impartial witness should be present during the entire informed consent discussion.

Certified translated ICFs will be provided by the sponsor in those languages required or requested by investigational sites.

After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to 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 during Screening 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. The basic elements of informed consent as specified in the ethical conduct provisions of US 21 CFR 50.25 (2011) and ICH E6 (2002) will be followed. 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 amendment will be implemented by qualified investigators under the sponsorship of Morphotek, Inc. (the sponsor) at approximately 20 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization (CRO) are listed on the Study Contact Sheet within the investigational site regulatory file provided to each site.

7 INTRODUCTION

Amatuximab (also known as MORAb-009) is a high-affinity monoclonal IgG1/κ antibody raised against human mesothelin. Mesothelin is a glycosylphosphatidylinositol-linked cytoplasmic membrane glycoprotein which is present in a restricted set of normal adult tissues, such as the mesothelium (Ordonez, 2003A). Immunohistochemistry has shown that mesothelin is overexpressed in virtually all mesotheliomas and pancreatic ductal adenocarcinomas and in a high percentage of epithelial ovarian cancers and non-small cell lung cancers (NSCLCs) (Ordonez, 2003B). Although the normal biological function of mesothelin is unknown, growing evidence suggests that it may play a role in tumorogenesis and metastasis (Kelly, et al., 2012). Its limited expression in normal human tissue and high expression in tumor makes mesothelin an excellent target antigen for antibody-based immunotherapy (Kelly, et al., 2012).

7.1 Indication

The indication under study is malignant pleural mesothelioma (MPM).

7.1.1 Current Therapeutic Options

MPM is an aggressive disease with poor prognosis. Although patients with a limited tumor burden may benefit from surgical resection, most patients have advanced disease at diagnosis and are not candidates for cytoreductive surgery (Sugarbaker, et al., 1996). For patients who are not eligible for curative surgery, the median survival with supportive care alone is 6 months whereas with the current standard treatment, a combination of cisplatin and pemetrexed, the median survival is 12 months (Vogelzang, et al, 2003) and this has not been improved upon by the addition of other investigational agents (eg, CBP501; Krug, et al., 2014). Various investigational agents are currently in clinical development for mesothelioma including immune checkpoint inhibitors.

7.1.2 MORAb-009 (Amatuximab)

7.1.2.1 Mechanism of Action

Mesothelin is a glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein which is present in a restricted set of normal adult tissues, such as the mesothelium (Ordonez, 2003A). Immunohistochemistry has shown that mesothelin is overexpressed in virtually all mesotheliomas and pancreatic ductal adenocarcinomas and in a high percentage of epithelial ovarian cancers and NSCLCs (Ordonez, 2003B). Although the normal biological function of mesothelin is unknown, growing evidence suggests that it may play a role in tumorogenesis and metastasis (Kelly, et al., 2012). Its limited expression in normal human tissue and high expression in tumor makes mesothelin an excellent target antigen for antibody-based immunotherapy (Kelly, et al., 2012).

Amatuximab is a high-affinity monoclonal IgG1/κ antibody raised against human mesothelin. Data from various in vitro and in vivo studies (Hassan, et al., 2007) indicate that amatuximab may have potential efficacy for the treatment of tumors which overexpress mesothelin. These data demonstrated the highly specific binding of amatuximab to target malignancies in vitro in immunohistochemistry staining studies. They also showed the biological activity of amatuximab on inhibiting mesothelin-bearing cell binding to the mesothelin ligand. Next, data demonstrated the capability of amatuximab to elicit an antibody-dependent cell-mediated cytotoxic response in vitro on mesothelin-bearing human tumor cells. In addition, it has been shown that amatuximab had positive in vivo data in a rodent xenograft model of mesothelin-overexpressing human cancer cells.

Results from these preclinical studies, nonhuman primate toxicology studies, and early-phase clinical studies indicate that amatuximab is a potentially useful anticancer agent (MORAb-009 Investigator's Brochure, 2014). Please refer to the Investigator's Brochure for additional information on the safety of amatuximab.

7.1.2.2 Clinical Experience With Amatuximab

As of January 2017, a total of 262 subjects have been exposed to amatuximab in Phase 1 or 2 studies. The clinical studies are summarized in the amatuximab Investigator's Brochure (MORAb-009 Investigator Brochure, 2014). No new safety or efficacy data was obtained from the current study 009-201 that was relevant to the Sponsor's determination to discontinue active enrollment.

7.1.2.2.1 PHASE 1 CLINICAL STUDIES

MORAb-009-001

This was a Phase 1, multiple-dose, open-label, dose-escalation cohort study conducted in subjects with advanced pancreatic adenocarcinoma, mesothelioma, mesothelin-expressing ovarian tumors, or NSCLC who had failed standard chemotherapy (Hassan, et al., 2010). A total of 24 subjects with advanced mesothelin-expressing tumors received doses of

12.5 mg/m^2 (n = 3), 25 mg/m^2 (n = 3), 50 mg/m^2 (n = 3), 100 mg/m^2 (n = 6), 200 mg/m^2 (n = 3), or 400 mg/m^2 (n = 6) of amatuximab, administered as IV infusions. Subjects received 4 weekly infusions on Days 1, 8, 15, and 22. After a 35-day treatment and observation period, subjects who had stable or improving disease by objective criteria could continue on treatment until disease progression occurred.

Of the 24 subjects, 13 had advanced mesothelioma, 7 had pancreatic cancer, and 4 had ovarian cancer. The median number of amatuximab infusions was 4 (range 1 to 24 infusions). Twenty subjects had tumor response assessments recorded. Of these, 11 subjects had stable disease (SD) recorded as their best overall tumor response, and 9 subjects had progressive disease (PD) recorded as their best overall response.

Of the 24 subjects who received amatuximab, 22 subjects (91.7%) reported a total of 120 treatment-emergent adverse events (TEAEs). The maximum tolerated dose (MTD) was determined to be 200 mg/m^2. At the 400-mg/m^2 dose level, 2 subjects experienced dose-limiting toxicities (Grade 4 transaminitis and Grade 3 serum sickness). Hypersensitivity AEs occurred in 7 of the 24 subjects. All hypersensitivity AEs were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.3.0 (2006) Grade 1 or Grade 2, with the exception of Grade 3 serum sickness in 1 subject. Thus, although other contributing causes of these AEs were present, 200 mg/m^2 was considered the maximum tolerated dose. Seven subjects had SD and received additional cycles of therapy, including 1 subject with previously progressive metastatic pancreatic cancer who received 6 additional cycles of amatuximab and demonstrated SD for over 6 months.

The results of this Phase 1 clinical trial in subjects with mesothelin-expressing advanced solid tumors demonstrated that amatuximab had an acceptable safety profile in these subjects, with a low incidence of immunogenicity. The single-agent maximum tolerated dose with weekly administration was 200 mg/m^2. Amatuximab serum concentrations increased in a dose-dependent fashion. While no objective responses were seen, disease stabilization was observed in several heavily pretreated subjects.

MORAb-009-006

This was a single-center, single-dose, open-label, pilot study of amatuximab, conducted in adult subjects with mesothelin over-expressing tumors to determine the biodistribution of ^{111}Indium (^{111}In)-labeled amatuximab in tumor and nontumor tissues in subjects with advanced mesothelin over-expressing cancers (pancreatic, mesothelioma, ovarian, or NSCLC). Subjects were required to have measurable disease that had progressed through prior therapy and that included a nonhepatic lesion for imaging that was ≥1.5 cm, as defined by modified Response Evaluation Criteria in Solid Tumors. Subjects received an initial 50-mg "cold" (ie, nonradiolabeled) dose of amatuximab followed by a single "hot" dose of ^{111}In-radiolabeled amatuximab (5 mCi) administered IV over 15 minutes. (Initially, unlabeled amatuximab [total dose 50 mg] was administered 0.5 to 6 hours prior to the radiolabeled test article to saturate any nonspecific binding and shed antigen. This unlabeled infusion was discontinued with the protocol amendment dated 12 Jul 2012; Data on file).

Serial single photon emission-computerized tomography (SPECT) imaging was performed at 2 to 4 hours, 24 to 48 hours, and 96 to 168 hours after the hot infusion to determine binding to tumor and nontumor tissue.

Six subjects (4 males; 2 females) were enrolled in the study (Data on file). Four subjects were diagnosed with mesothelioma and 2 with pancreatic adenocarcinoma. Five subjects received both an initial 50-mg "cold" (ie, nonradiolabeled) dose of amatuximab and a single "hot" dose of ^{111}In-radiolabeled amatuximab; 1 subject enrolled after the protocol amendment of 12 Jul 2012 and received only the "hot" dose of amatuximab. All 6 enrolled subjects completed the study.

Of the 6 subjects who received amatuximab, 1 subject experienced 4 AEs: nausea, shoulder pain, and 2 events of pyrexia.

^{111}In-radiolabeled amatuximab was shown to be effective in producing sufficient Tumor: Background ratio activity in mesothelioma and pancreatic cancer tumors with a favorable dosimetry profile. Higher uptake was seen in the mesotheliomas as compared with the pancreatic cancers.

MORAb-009-J081-102

This was a multiple-dose, open-labeled Phase 1 study (MORAb-009-J081-102) in Japan to assess the safety of amatuximab at doses of 50, 100, and 200 mg/m^2 in subjects with solid tumors (Data on file). Amatuximab was administered over 4-week cycles, with infusions once weekly on Days 1, 8, 15, and 22. From Cycle 2 onward, amatuximab administration was allowed to be continued at the same dosing regimen unless subjects met the discontinuation criteria.

A total of 17 subjects entered the study and received at least 1 dose of amatuximab; 7 subjects each in the 50 and 200 mg/m^2 groups and 3 subjects in the 100 mg/m^2 group. A total of 17 subjects were enrolled, 12 males and 5 females. The median age was 62.0 years (range: 56 to 79 years) (Data on file). The tumor types reported at Screening (primary disease at first diagnosis) were colorectal cancer (7 subjects, 41.2%), pancreatic adenocarcinoma (6 subjects, 35.3%), head and neck cancer and mesothelioma (2 subjects each, 11.8%).

Of the 17 subjects who received amatuximab, 15 subjects (88.2%) experienced TEAEs, and 13 subjects (76.5%) experienced TEAEs that were considered related to administration of Test Article. TEAEs of Grade 3 or 4 were reported in 9 subjects (52.9%). There were no apparent dose-related trends in frequency or severity of TEAEs. The most frequently reported TEAEs in the total group (N = 17) were fatigue (8 subjects; 47.1%); pyrexia (7 subjects; 41.2%); aspartate aminotransferase increased and decreased appetite (6 subjects each; 35.3%); vomiting and somnolence (5 subjects each; 29.4%); and nausea, blood lactate dehydrogenase increased, and weight decreased (4 subjects each; 23.5%). The most frequently reported treatment-related adverse events (TRAEs) in the total group (N = 17) were fatigue (5 subjects; 29.4%) and pyrexia (4 subjects; 23.5%).

One subject in the 200 mg/m^2 group experienced Grade 5 interstitial lung disease, and 1 subject in the 50 mg/m^2 group experienced Grade 4 blood bilirubin increased. The most frequently reported TEAEs of Grade 3 or higher in the total group (N = 17) were hyperglycemia and hyponatremia (2 subjects each; 11.8%). TRAEs with Grade 3 or higher were interstitial lung disease (1 subject; 5.9%, Grade 5) and cytokine release syndrome (1 subject; 5.9%, Grade 3).

There were no apparent dose-related trends in frequency or severity of TEAEs for the whole treatment period.

Eight subjects (47.1%) experienced a total of 14 treatment-emergent serious adverse events (SAEs) in this study, and SAEs in 3 subjects (3 events) were considered to be related to study drug. The most frequently reported SAEs were jaundice and cytokine release syndrome (2 subjects each; 11.8%).

Five subjects (29.4%) experienced adverse events of interest (AEIs) classified by the investigators during the study. The most frequently reported AEIs were cytokine release syndrome (3 subjects; 17.6%), and pyrexia and hot flush (2 subjects each; 11.8%).

Dose-limiting toxicities were reported in 2 subjects; 1 subject in the 50 mg/m^2 group experienced Grade 3 cytokine release syndrome, and 1 subject at 200 mg/m^2 experienced Grade 5 interstitial lung disease.

During the study, anti-drug antibodies (ADA) were detected in 8 of 17 subjects. During treatment, ADA were detected in 4 of 4 subjects without premedication and in 4 of 13 subjects with premedication.

Based on the criteria as defined in the protocol, tolerability of amatuximab at 50, 100, and 200 mg/m^2 was confirmed. The MTD of this study was determined to be 200 mg/m^2. However, the actual MTD of amatuximab might be higher than 200 mg/m^2, since a dose above 200 mg/m^2 was not investigated in this study.

7.1.2.2.2 PHASE 2 CLINICAL STUDIES

MORAb-009-002

MORAb-009-002 was a randomized, placebo-controlled, double-blind Phase 2 study. Eligible subjects were randomized to receive amatuximab 5 mg/kg plus gemcitabine 1000 mg/m^2 once weekly or placebo plus gemcitabine 1000 mg/m^2 once weekly (Data on file). Cycle 1 was 8 weeks in duration, with treatment administration on Day 1 of Weeks 1 through 7; no study medication was administered in Week 8. Cycle 2 and all subsequent cycles were 4-week cycles with study drug administration on Day 1 of Weeks 1 through 3; no study medication was administered on Week 4. A total of 155 subjects were randomized to the study (77 to amatuximab and 78 to placebo); 148 subjects (73 on amatuximab, 75 on placebo) received at least 1 dose of study medication.

Based on the results of the primary analysis, amatuximab was not statistically superior to placebo in overall survival (OS). The 2 treatment groups were comparable with respect to key secondary endpoints of objective response rate (ORR) and progression-free survival (PFS).

The safety profiles of the 2 regimens were similar. All 73 subjects who received amatuximab experienced at least 1 AE. A greater percentage of subjects in both the amatuximab (94.5%) treatment group and the placebo (89.3%) treatment group had AEs considered related to chemotherapy administration compared with AEs considered related to amatuximab (67.1%) or placebo (60.0%) administration. This was also true for Grade 3 or higher AEs. A total of 21 (28.8%) subjects receiving amatuximab and 17 (22.7%) subjects receiving placebo experienced AEs resulting in discontinuation of study medication. A total of 25 (34.2%) subjects receiving amatuximab experienced hypersensitivity AEs during the study compared with 16 subjects receiving placebo (21.3%). A hypersensitivity AE for 1 subject receiving amatuximab was classified as a possibly-related SAE, and 1 subject receiving placebo had a hypersensitivity AE that was classified as an unrelated SAE. All other hypersensitivity AEs were Grade 2 or less in severity. As hypersensitivity AEs are expected with administration of a chimeric monoclonal antibody, the hypersensitivity AEs in this study were anticipated. SAEs of thrombocytopenia, neutropenia, and anemia were primarily considered related to gemcitabine administration. The addition of amatuximab did not negatively affect these laboratory values (Data on file).

A preliminary exposure-response analysis was conducted on this study which revealed that, across all subjects (placebo and amatuximab), amatuximab exposure was not a significant predictor of either PFS or OS.

These data, plus the preliminary data from the 2 subjects with pancreatic cancer in the ^{111}In-radiolabeled amatuximab study, may help explain the lack of difference in the results of adding amatuximab to gemcitabine as compared to placebo plus gemcitabine.

MORAb-009-003

MORAb-009-003 was an open-label, Phase 2 study adding amatuximab, 5 mg/kg administered on Days 1 and 8, to the combination of pemetrexed, 500 mg/m^2, and cisplatin, 75 mg/m^2, administered on Day 1 of 21-day cycles for up to 6 cycles in the treatment of systemic-therapy-naïve subjects with unresectable MPM (Data on file). For those subjects who completed at least 4 cycles of the Combination Therapy and had not progressed, they were allowed to enroll in the single-agent Maintenance Therapy phase. Eighty-nine subjects were enrolled. The median age of the subjects was 67 years; 77.5% were male, and 88% had stage III/IV disease. The median number of amatuximab plus pemetrexed and cisplatin cycles administered to these subjects was 5 (range 1-7); single-agent amatuximab was administered to 56 (62.9%) subjects. The Kaplan-Meier estimate of 6 month PFS was 59.3% (95% CI: 47.1, 69.6) which did not meet the primary efficacy objective for this study. The median PFS was 6.3 months (95% CI: 6.0, 7.8).

Although the median PFS was not significantly different from the historical results of pemetrexed and cisplatin alone, the median OS in this study was 14.8 months (95% CI: 12.4, 18.8), which is 6 to 8 weeks longer than expected from the historical results of pemetrexed/cisplatin. There were no complete responses (CR). Twenty-nine subjects (34.5%) had partial responses (PR) (ORR: 34.5% [95% CI: 24.5, 45.7]) and 47 subjects (56%) had stable disease as the best response. The disease control rate (DCR) was 90.5%. As of the end of study, 05 Dec 2013, 11 subjects were still living.

Among the most common AEs seen in ≥ 15% of subjects during the Combination Therapy phase were nausea (71%), fatigue (58%), anorexia (45%), vomiting (32%), constipation (32%), anemia (29%), neutropenia (29%), diarrhea (28%), and weight decrease (19%). Hypersensitivity reactions (12%) as well as infusion related reactions (8%) were also seen. The SAEs during the Combination Therapy phase were hypersensitivity reactions (4 subjects), neutropenia (4 subjects), atrial fibrillation (4 subjects), hyponatremia (3 subjects), anemia (3 subjects), dehydration (2 subjects), fatigue (2 subjects), noncardiac chest pain (2 subjects), pyrexia (2 subjects), and pneumothorax (2 subjects). AEs which led to discontinuation of treatment were: hypersensitivity reactions to amatuximab (8 subjects), increasing serum creatinine (6 subjects), fatigue (3 subjects), neutropenia (2 subjects), worsening in the subjects' general condition (2 subjects), nausea and vomiting (2 subjects), development of a pneumothorax (2 subjects), and 1 subject each for anemia, thrombocytopenia, dyspnea, pericarditis and pericardial effusion.

During the amatuximab Maintenance Therapy phase, the most common AEs (seen in more than 15% of subjects) were dyspnea (32%), nausea (25%), noncardiac chest pain (23%), fatigue (20%), and peripheral neuropathy (18%). SAEs seen during the Maintenance Therapy phase were dyspnea (4 subjects) and fatigue (1 subject). AEs which led to discontinuation of treatment were hyperbilirubinemia (1 subject), peritonitis (1 subject), and cardiopulmonary arrest (1 subject). The latter was reported in a 58-year old PPD who suffered a cardiac arrest related to cocaine use, 1 week after the first dose of maintenance amatuximab, from which PP was successfully resuscitated.

AEIs for this study were defined as: Cytokine Release Syndrome; Flushing; Fever; Rigors/chills; Sweating/diaphoresis; Pruritus/itching; Urticaria; Bronchospasm/wheezing; and Bronchial edema. In addition, Drug Hypersensitivity Adverse Events (DHAE) were defined as the subset of programmatically-identified AEIs that have serologic evidence of an immunologic response to amatuximab (ie, positive human anti-drug antibody [ADA] which are defined as a treatment-induced or treatment-boosted ADA). The determination of DHAE status for each of the programmatically-identified AEIs described above was dependent on serum ADA sample results obtained on or subsequent to the onset date of the AEI. There could be multiple subsequent ADA samples. If the serum ADA results are positive for at least 1 of these samples, the AEI was considered a DHAE.

A total of 54 DHAEs in 25 (28.1%) subjects receiving amatuximab/pemetrexed/cisplatin combination therapy and 19 DHAEs in 7 (12.5%) subjects receiving single-agent maintenance were reported. In the subjects receiving combination therapy, the most common

DHAEs were chills (9 subjects, 10.1%), hypersensitivity (9 subjects, 10.1%), and infusion-related reaction (6 subjects, 6.7%). In the subjects receiving single-agent maintenance therapy, the most common DHAEs were chills (3 subjects, 5.4%), dyspnea (2 subjects, 3.6%) and infusion-related reaction (2 subjects, 3.6%). Seven (7.9%) DHAEs resulted in subject discontinuation from amatuximab. The majority of DHAEs occurred after infusion 3 (25 events in 15 subjects) or infusion 4 (24 events in 17 subjects). None were reported beyond infusion 20.

Population Pharmacokinetics

Results of the population pharmacokinetics (PK) study of amatuximab (Gupta, et al., 2014; MORAb-009 Investigator's Brochure, 2014) were as follows:

- The PK of amatuximab following IV infusion was adequately described by a 2 compartment model with parallel linear and nonlinear elimination over the dose range of 12.5 to 400 mg/m^2
- Body weight was identified to affect volume of distribution of the central compartment
- The presence of human ADA, as defined by the presence of ADA at a titer of greater than 64, was found to increase linear clearance which would result in lower concentrations of amatuximab
- Median serum concentration time profile of amatuximab indicates that after 5 weeks of continuous weekly dosing 89% of steady-state concentration is achieved
- After taking into account the effect of weight, age (33 – 90 years), race (Japanese vs. non-Japanese), and gender did not influence amatuximab PK
- Baseline albumin (2.38 – 5.46 g/dL) did not influence amatuximab PK

Preliminary Pharmacokinetic/Pharmacodynamic Analyses of Amatuximab Efficacy in MORAb-009-003

Results of the Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Amatuximab Efficacy study (Gupta, et al., 2014; MORAb-009 Investigator's Brochure, 2014) were as follows:

- Amatuximab minimum observed serum concentrations (C_{min}) were a significant predictor of both PFS and OS where higher concentrations were associated with longer PFS and OS. Subjects achieving C_{min} concentrations above median had a median PFS and OS of 238 and 583 days, respectively.
- Based on the multivariate parametric survival model, amatuximab exposure was a significant predictor of OS in the presence of an effect of baseline Karnofsky Performance Status score and tumor type
- Results of the PK simulations showed that 5 mg/kg of amatuximab, administered weekly, will achieve median C_{min} concentration of 83.1 μg/mL, and approximately 80% of subjects would be above the C_{min} of 38.2 μg/mL by 28 days of 5 mg/kg weekly dosing

- Weekly administration of amatuximab, 5 mg/kg, would lead to higher C_{min} concentrations which may lead to a statistically significant and clinically meaningful benefit in OS, as well as PFS, versus the standard therapy of pemetrexed plus cisplatin in subjects with unresectable MPM

7.1.2.3 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Amatuximab and Study Drug Exposure

The following symptoms and signs are expected to occur commonly in this study population, and may result in a SAE: noncardiac chest pain, cough, dyspnea, pleural effusion and pneumothorax (NCCN, 2013).

The following AEs have been commonly seen with the use of pemetrexed in combination with cisplatin: vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia and constipation (Alimta, 2013).

7.2 Study Rationale

On 11Jan2017, Eisai notified study investigators that the decision was made to discontinue further enrollment in the study and significantly amend the protocol to discontinue all ongoing study procedures and conduct, but provide a mechanism for patients already randomized to the amatuximab (MORAb-009) arm to continue to receive ongoing study treatment until discontinuation for disease progression or tolerability issues. Per the amendment, only core information necessary for safety monitoring and reporting will be collected. No efficacy data will be reported. Subjects who were randomized to placebo and all subjects in follow-up have been discontinued from the study.

The principal factor driving this business decision was significant delays in initiating the program, which led to a significant shift in the timing of the primary and final analyses. As a result, the original rationale for the study is now compromised by the introduction of newer treatment regimens (eg, bevacizumab) and the rapid clinical development of several investigational agents (eg, immune checkpoint inhibitors), such that the program no longer aligns with the developing standard of care.

It is important to note that there have been no new safety issues identified during the conduct of this study to date that are driving this decision. There is also no new efficacy data that informed this decision.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this amendment is to provide ongoing amatuximab treatment access consistent with the primary 009-201 treatment schedule to those trial subjects randomized to the amatuximab arm who, at the discretion of their investigator, may obtain ongoing clinical benefit.

8.2 Secondary Objectives

The secondary objective of this amendment is to monitor safety of ongoing subjects through the collection of SAEs.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

The primary 009-201 study was designed as a multicenter, double-blind, randomized, placebo-controlled study designed to demonstrate the safety and efficacy of amatuximab in subjects with unresectable MPM who have not received prior systemic therapy. Subjects were randomly assigned to receive weekly administration of either amatuximab, 5 mg/kg, or placebo in combination with pemetrexed, 500 mg/m^2, and cisplatin, 75 mg/m^2, on Day 1 of each 21-day cycle for 6 cycles followed by single-agent test article maintenance until disease progression. All subjects were to be followed for OS.

On 11Jan2017 Eisai notified investigators of a business decision to discontinue any further enrollment in the study and significantly amend the protocol as described previously.

Per this amendment, subjects enrolled in the study who were randomized to amatuximab and are still on active treatment may consent to continue to receive amatuximab at the discretion of the PI until disease progression, intolerable toxicity, or withdrawal of consent.

Clinical management and ongoing assessments of subjects will continue per standard of care as determined by the PI. Only serious adverse event and subject discontinuation data will be collected by the Sponsor. Subjects will not be followed for efficacy. Subjects randomized to placebo and all subjects in follow-up have been discontinued from the study.

At the time enrollment was closed 108 subjects were randomized, 27 to the amatuximab treatment arm.

9.1.1 Screening Phase

The screening phase of the study is complete.

9.1.2 Randomization/Combination Treatment Phase

Subjects who were eligible for this study were randomized in a 1:1 ratio to receive blinded treatment with either amatuximab or placebo (ie, Test Article). All enrolled subjects were also assigned to receive the standard-of-care treatments pemetrexed and cisplatin (ie, Study Drugs) for six cycles. Per this amendment, only those active subjects randomized to amatuximab are continuing.

If the subject develops unacceptable toxicity to Study Drugs (pemetrexed or cisplatin) and has completed at least 4 cycles (but no more than 6 cycles) during the Combination Treatment phase, the subject is eligible to continue on to the Maintenance Treatment Phase (see below).

9.1.2.1 Test Article Administration (Amatuximab) Only Visits

Test Article administration only visits will be performed when the Study Drugs (pemetrexed and cisplatin) are delayed. For specific details on Test Article administration only visits, please see the Schedule of Procedures/Assessments.

9.1.3 Maintenance Treatment Phase

Subjects who have not progressed following completion of Combination Treatment will enter the Maintenance Treatment Phase where they will continue to receive amatuximab on a weekly basis until disease progression. For specific details on the Maintenance Treatment Phase, refer to the Schedule of Procedures/Assessments.

9.1.4 End of Treatment Visit

Upon discontinuation of treatment for documented disease progression or any other reason, assessments for the End of Treatment Visit should be performed. These assessments will be conducted (where possible) within 7 days of the last dose of amatuximab. For specific details on the End of Treatment Visit, refer to the Schedule of Procedures/Assessments.

9.1.5 Follow-Up Phase

Following discontinuation of treatment subjects will have a 30-day follow-up visit for assessment of adverse events. All adverse event information must be documented in the subject's medical record (source data). Only SAEs need to be reported to the Sponsor.

9.1.6 End of Study

The 30-day follow-up visit will also constitute the End of Study visit.

9.2 Selection of Study Population

9.2.1 Inclusion Criteria

All subjects were enrolled under the inclusion criteria outlined in protocol version 2.0, dated 24 Apr 2015. The following criteria apply to this amendment:

1. Subjects who were enrolled in the study and randomized to the amatuximab treatment arm may, at the discretion of the PI, consent to continue to receive amatuximab therapy until disease progression, intolerable toxicity, or withdraw of consent.

2. Subjects of childbearing potential must be surgically sterile or consent to use a highly effective method of contraception throughout the study period. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, 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). If a patient of childbearing potential is neither surgically sterile nor postmenopausal, highly effective contraceptive measures must start either prior to or at Screening and continue throughout the entire study period and for at least 6 months after the last dose of chemotherapy and at least 30 days after the last dose of amatuximab is administered (whichever is later). A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Periodic abstinence, the rhythm method, the withdrawal method, condoms, and diaphragms are not acceptable methods of contraception. Women of childbearing potential must also refrain from egg cell donation for 6 months after the final dose of investigational product.
3. 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 throughout the study period and for 6 months after discontinuation of chemotherapy and for 5 weeks after amatuximab discontinuation [whichever is later]). No sperm donation is allowed during the study period and for 90 days after amatuximab discontinuation.

9.2.2 Exclusion Criteria

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

1. Subjects previously randomized to placebo
2. Subjects who have not signed the updated informed consent form associated with this amendment
3. Subjects who have radiographic or clinical disease progression, or intolerable toxicity such that ongoing amatuximab treatment through this study is not appropriate

9.2.3 Removal of Subjects From Therapy or Assessment

The investigator will discontinue a subject's study treatment (chemotherapies and/or amatuximab) or withdraw the subject from the study if any of the following circumstances occur at any time during the subject's study participation:

- The subject's continued participation, in the investigator's judgment, would be detrimental to his/her health

- The subject withdraws consent for continued participation or refuses further treatment with the study agent(s)
- The subject experiences an intolerable toxicity not ameliorable by symptomatic treatment or dose schedule modification
- The subject has objective evidence of disease progression or symptomatic deterioration (ie, global deterioration of health status)
- The subject experiences development or exacerbation of a recurrent illness or other factors that results in a delay of the next scheduled treatment by 21 days or more
- The subject experiences a hypersensitivity AE of NCI CTCAE v4.03 (2010) Grade 3 that cannot be medically managed to a level of Grade 2 (see Section 9.4.1.4.3 and Appendix 1)
- The subject experiences a hypersensitivity reaction of Grade 4 (see Section 9.4.1.4.3 and Appendix 1)
- The subject receives other anticancer therapy (eg, chemotherapy or radiotherapy; however, local radiotherapy of noncurative intent is allowed) during the Combination Treatment or Maintenance Treatment phases
- The subject becomes pregnant

If a subject withdraws consent, the date will be documented in the source documents. The End of Treatment and End of Study procedures will be completed and the primary reason for discontinuation from treatment will be documented in the source records and reported to the Sponsor.

9.3 Treatments

Subjects continuing in the study will receive the experimental drug amatuximab. "Study Drug" refers to any drug(s) or formulations under evaluation in the study, including the Test Article, active controls, and placebo. The Study Drugs in this study are amatuximab, pemetrexed, and cisplatin.

9.3.1 Treatments Administered

All subjects will receive Combination Treatment for six 21-day cycles. Amatuximab 5mg/kg will be administered IV once weekly. The Study Drugs, pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, will be administered on Day 1 of each 21-day Combination Treatment cycle for 6 cycles. On Day 1 of each cycle, amatuximab will be administered prior to pemetrexed, which will be administered prior to cisplatin.

Subjects who have completed a minimum of 4 cycles of Combination Treatment and who have not progressed will enter the Maintenance Treatment Phase where they will continue to receive amatuximab on a weekly basis until radiographic disease progression occurs.

Always premedicate subjects to prevent hypersensitivity AEs. Subjects must be premedicated approximately 30 to 60 minutes prior to each infusion of amatuximab with acetaminophen 650 mg by mouth and diphenhydramine 25 to 50 mg by mouth or IV, or

clinical equivalent per clinic routine and country availability. Refer to Section 9.3.7.1.1 for additional details on premedications for amatuximab.

Refer to Section 9.3.7.1.2 for additional details on premedications for pemetrexed.

The following treatments will be administered to subjects continuing in this study (Table 1).

Table 1 Treatments Administered

Drug Name	Dose	Route of Administration	Dose Schedule
Combination Treatment Phase			
Amatuximab	5 mg/kg	IV infusion	Once weekly for six 21-day cycles
Plus			
Chemotherapy			
Pemetrexed	500 mg/m^2	IV infusion	Day 1 of each 21-day cycle for 6 cycles
Cisplatin	75 mg/m^2	IV infusion	Day 1 of each 21-day cycle for 6 cycles
Maintenance Treatment Phase			
Amatuximab	5 mg/kg	IV infusion	Once weekly until disease progression

IV = intravenous.

9.3.2 Identity of Investigational and Noninvestigational Products

9.3.2.1 Amatuximab

The investigational product, amatuximab, is supplied as a 25 mg/mL solution in 10-mL vials. It is a chimeric (mouse/human) IgG1/κ antibody that binds to the human mesothelin protein.

The formulation to be used in this clinical trial is presented in Table 2 (MORAb-009 Investigator's Brochure, 2014).

Table 2 Formulation of Amatuximab

Investigational product	Amatuximab (MORAb-009)
Formulation	20 mM glutamate/200 mM sorbitol, ph 5.0 (pharmaceutical grade)
Strength	25 mg/mL
Route of administration	Intravenous infusion
Manufacturer	Lonza Inc., Slough , UK

9.3.2.2 Pemetrexed

Pemetrexed, a noninvestigational product for this study, is to be administered to all study subjects, regardless of randomization assignment. Pemetrexed will be supplied by the investigational site unless prohibited by local regulations or institutional policy. It is a sterile lyophilized powder for IV infusion. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial contains pemetrexed disodium equivalent to 500 mg of pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

9.3.2.3 Cisplatin

Cisplatin, a noninvestigational product for this study, is to be administered to all study subjects, regardless of randomization assignment. Cisplatin will be supplied by the investigational site unless prohibited by local regulations or institutional policy. It is a sterile aqueous solution. Each mL contains 1 mg of cisplatin and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide are added to adjust pH of the solution.

9.3.2.4 Chemical Name, Structural Formula of Investigational Product

Not applicable.

9.3.2.5 Labeling for Investigational Product

Amatuximab 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.

9.3.2.6 Storage Conditions

Study Drugs (pemetrexed and cisplatin) must be stored as instructed on the label.

Amatuximab must be kept in a secure location and carefully stored at 2°C to 8°C at the investigational site in its original container and protected from light. Note that all relevant site-specific guidelines and country-specific labeling requirements must be followed. 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.

The dose of amatuximab required for a subject is to be taken from as many vials as required. Any amatuximab remaining in a vial after withdrawing a subject's dose is not to be used for subsequent doses.

Additional details on the storage, handling, and inventory of amatuximab will be provided in the Pharmacy Manual.

9.3.3 Method of Assigning Subjects to Treatment Groups

Subjects were assigned to treatments based on a computer-generated randomization scheme that was reviewed and approved by a statistician.

9.3.4 Selection of Doses in the Study

The 5-mg/kg dose of amatuximab was selected based on the results of the MORAb-009-003 study and on the results of exposure-response analysis. The selection of the dose of pemetrexed as well as cisplatin is based on the country-specific labeling requirements.

9.3.5 Selection and Timing of Dose for Each Subject

Amatuximab will be administered on a once-weekly schedule. Detailed instructions for the preparation, dilution, and administration of amatuximab are provided in the Pharmacy Manual. The selection of the dosing schedule for pemetrexed and cisplatin is based upon the country-specific labeling requirements.

At Week 1, Day 1 of each 21-day cycle, the amatuximab) will be administered, followed by the chemotherapy (pemetrexed [500 mg/m^2] and then cisplatin [75 mg/m^2]). The dosage for the chemotherapy will be calculated at Cycle 1, Week 1, Day 1 and adjusted per the country-specific labeling requirements. In the event that the chemotherapy regimen is discontinued before the subject reaches the 4th cycle, the subject will discontinue amatuximab administration and be discontinued from the study.

Dose reductions can be considered if subjects experience AEs related to the chemotherapy (pemetrexed and cisplatin). Dose reductions for toxicities can be made per country-specific labeling requirements.

To date, no AEs attributed to amatuximab have been demonstrated to be dose-related. Therefore, no prescribed dose alterations and no dose modifications of amatuximab are planned.

9.3.6 Blinding

This study has been unblinded. Each investigator site has been provided with a list of their subject numbers and the treatment arm to which each subject was assigned in order to inform future medical management decisions.

9.3.7 Concomitant Therapy

Any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of amatuximab will be

recorded in the subject's medical record. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with amatuximab, pemetrexed, or cisplatin may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) amatuximab, pemetrexed, or cisplatin.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell counts.

9.3.7.1 Premedications

All premedications for amatuximab and Study Drugs must be reported in the subject's medical record.

9.3.7.1.1 PREMEDICATIONS FOR AMATUXIMAB

Subjects must be premedicated to prevent hypersensitivity AEs. To date, hypersensitivity AEs have been observed in the Phase 1 trials as well as in both of the Phase 2 trials. In order to prevent or to reduce the incidence and severity of these types of hypersensitivity AEs, all subjects must be premedicated approximately 30 to 60 minutes prior to each infusion of amatuximab with acetaminophen 650 mg by mouth and diphenhydramine 25 mg to 50 mg by mouth or IV, or clinical equivalent per clinic routine and country availability. Should hypersensitivity AEs occur in spite of these premedications, other suggested treatment regimens (ie, secondary prophylaxis of hypersensitivity AEs), are provided below.

The recommendations below for secondary prophylaxis are based on observations made on the Phase 1 and Phase 2 trials conducted to date and on standard clinical practice. For subjects experiencing any hypersensitivity AEs, secondary prophylaxis is recommended and will be given at the investigator's discretion:

- Grade 1 Events: Subjects experiencing hypersensitivity AEs consisting of Grade 1 events can be managed with secondary prophylaxis for subsequent infusions. Along with an antipyretic of choice (acetaminophen up to a dose of 1000 mg by mouth has been used) and concurrent use of diphenhydramine, an H2 receptor antagonist can be considered, such as ranitidine (50 mg IV). Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with amatuximab

• Grade 2 Events: Subjects experiencing hypersensitivity AEs consisting of Grade 2 events can be managed with secondary prophylaxis for subsequent infusions, along with diphenhydramine 50 mg IV, ranitidine 50 mg IV, and dexamethasone 20 mg IV. Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with amatuximab.

Secondary prophylaxis regimens above are recommendations to be given at the investigator's discretion and should be recorded in the subject's medical record.

• Grade 3 and Grade 4 Events: If a Grade 3 hypersensitivity AE occurs, the subject may be continued at the discretion of the investigator, provided the AE can be reduced to and maintained at Grade 2 or lower. In the event that a Grade 4 hypersensitivity AE occurs, the subject will be discontinued from treatment with amatuximab and discontinued from the study.

9.3.7.1.2 PREMEDICATIONS FOR PEMETREXED

Subjects must receive prophylactic treatment for pemetrexed with folic acid, vitamin B12, and dexamethasone at each cycle of Combination Treatment according to the investigational site's standard practice. As a general guideline, starting at least 5 days prior to the first dose of pemetrexed, subjects will begin treatment with folic acid and vitamin B12 (refer to the Schedule of Procedures/Assessments. Folic acid will be administered at a dose in the range of 350 µg to 1 mg by mouth daily. Vitamin B12 will be administered by intramuscular injection at a dose of 1 mg approximately every 9 weeks. Dexamethasone will be administered at a dose of 4 mg by mouth twice daily for 3 days as follows: the day before, the day of, and the day following each infusion of pemetrexed. (Refer to the country-specific labeling requirements.)

9.3.7.2 Drug-Drug Interactions

Not applicable.

9.3.7.3 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies (eg, chemotherapy, radiotherapy, nonstudy monoclonal antibodies, immunomodulators, or immunotherapy) or cytotoxic therapy (eg, methotrexate for rheumatoid arthritis) while in the Combination treatment or Maintenance Treatment phases; however, local radiotherapy for noncurative intent is allowed. If subjects receive additional antitumor therapies, this will be judged to represent evidence of disease progression, and all study drugs will be discontinued.

9.3.8 Treatment Compliance

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

Amatuximab is to be dispensed only to subjects enrolled in the clinical trial. Infusions of the amatuximab are to be administered by appropriately trained and qualified personnel.

9.3.9 Drug Supplies and Accountability

The pharmacist (or qualified designee, as appropriate) will be responsible for the accountability of all study treatments/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the amatuximab to be used other than as directed by this protocol. Amatuximab 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 amatuximab, dispensing of amatuximab to the subject, collection and reconciliation of unused amatuximab that are shipped to site but not dispensed to subjects, and return of reconciled amatuximab to the sponsor or (where applicable) destruction of reconciled amatuximab at the site. This includes, but may not be limited to: (a) documentation of receipt of amatuximab, (b) Amatuximab dispensing/return reconciliation log, (c) Amatuximab accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) documentation of destruction for any destruction of amatuximab/study supplies that occurs at the site, where available. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The amatuximab 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, Medicines and Healthcare Products Regulatory Agency).

Drug accountability will be reviewed during site pharmacy visits and at the completion of the study by the unblinded CRA.

As permissible by site standards, and after drug accountability has been performed by the unblinded CRA, empty and partially used amatuximab vials are to be destroyed by the site. Destruction will occur following the site's standard procedures and documentation of destruction will be maintained. If destruction on site is not allowed, arrangements can be made to return used vials to the depot.

At the conclusion of the study or by sponsor directive, and upon completion of drug accountability and reconciliation procedures by the site's unblinded personnel and review by the unblinded CRA, any unused vials of amatuximab that were shipped to the site but not administered to subjects must be destroyed by the site or boxed, sealed, and shipped back to the sponsor's designated central or local depot, following all local regulatory requirements. In some regions, the amatuximab may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

9.4 Study Assessments

9.4.1 Assessments

9.4.1.1 Screening Assessments

All continuing subjects have completed screening assessments as outlined in protocol version 2.0, date 24 Apr 2015.

9.4.1.2 Efficacy Assessments

No further efficacy assessments are required.

9.4.1.2.1 FOLLOW-UP FOR SURVIVAL

No longer applicable.

9.4.1.2.2 COMPUTED TOMOGRAPHY SCAN OR MAGNETIC RESONANCE IMAGING

Investigators may continue to perform CT or MRIs at their discretion per standard clinical practice. No further images or data will be collected by the Sponsor.

9.4.1.2.3 QUALITY OF LIFE ASSESSMENT (LCSS-MESO)

No further assessments are required.

9.4.1.2.4 PERFORMANCE STATUS (DPSM)

No further assessments are required.

9.4.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.4.1.3.1 PHARMACOKINETIC ASSESSMENTS

Samples collected to date may be analyzed. No further samples will be collected.

9.4.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Pharmacodynamics

No longer applicable.

Pharmacogenomics

Samples already collected will be stored and analyzed per the terms of the original informed consent form signed by each subject. No additional samples will be collected.

Biomarkers

Samples already collected will be stored and analyzed per the terms of the original informed consent form signed by each subject. No additional samples will be collected.

9.4.1.4 Safety Assessments

Safety assessments will consist of recording all AEs, including all CTCAE v4.03 grades (for both increasing and decreasing severity), all AEIs, and SAEs; regular monitoring of hematology, and blood chemistry values; regular monitoring of ECGs; periodic measurement of vital signs; and performance of physical examinations at the discretion of the investigator per standard of care.

Assessments will be documented in subject's medical records and only SAEs will be reported to the Sponsor.

9.4.1.4.1 Adverse Events and Other Events of Interest

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the Study Drugs.

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
- Any new disease or exacerbation of an existing disease; however, worsening of the primary disease is considered disease progression rather than 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 amatuximab and/or chemotherapy
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (ie, prior to the first administration of amatuximab)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be documented beginning from the time the subject signs the study ICF through the last visit and for 30 days after the subject's last dose of amatuximab. 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.

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 500 ms and there is an increase of more than 30 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be documented as such.

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

Per this amendment all adverse events will documented in the subject's medical record. Only AEs meeting the criteria of serious as described in Section 9.4.1.4.2 will be reported to the Sponsor per Section 9.4.3.

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

Assessing Severity of Adverse Events

AEs will be graded on a 5-point scale according to CTCAE v4.03. Investigators will document CTCAE grades for all AEs.

Assessing Relationship to Study Drugs

Items to be considered when assessing the relationship of an AE to the study drug(s) are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, especially the effect of discontinuation of study drug(s) or reintroduction of study drug(s), as applicable
- Whether the event is known to be associated with the study drug 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 in the subject's medical record 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.

9.4.1.4.2 Serious Adverse Events and Other Events of Interest

A SAE is any untoward medical occurrence that at any dose:

- Results in death (other than death due to PD as this is the study endpoint)
- Is life-threatening (ie, the subject was at immediate risk of death from the AE 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 inpatient 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.

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; and AEs associated with study drug overdose, misuse, abuse, or medication error. These events of interest 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 events of interest are to be reported in the subject's medical record 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 for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after 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

Death due to disease progression is a study endpoint, and is therefore not considered an SAE in this study and does not need to be reported as such.

9.4.1.4.3 ADVERSE EVENTS OF INTEREST

The conditions of hypersensitivity AEs and interstitial lung disease AEs are possible with administration of any monoclonal antibody and should be considered AEIs.

Hypersensitivity

The following signs and symptoms are considered hypersensitivity AEs if they occur within 24 hours of infusion:

- Cytokine release syndrome
- Flushing
- Fever
- Rigors/chills
- Sweating/diaphoresis
- Pruritus/itching
- Urticaria
- Bronchospasm/wheezing
- Bronchial edema

An abbreviated NCI CTCAE v.4.03 for grading some of the most commonly observed hypersensitivity AEs has been provided in Appendix 1. Refer to the full NCI CTCAE v.4.03 for complete event grading information. All hypersensitivity AEs are to be recorded in the subject's medical record. Hypersensitivity AEs that meet the definition of a SAE should also be reported in an expedited fashion using the SAE form as well in the same manner and timeframe as reporting of SAEs (Section 9.4.3.1).

Hypersensitivity AEs have been seen in the Phase 1 and 2 clinical trials of amatuximab during and immediately following the administration of amatuximab. In general, hypersensitivity AEs to monoclonal antibodies are immediate, typically occurring during the first few minutes of the first infusion. However, up to 30% of reactions to monoclonal antibodies are delayed and may occur in later infusions (Lenz, 2007).

Treatment of Hypersensitivity AEs

If a hypersensitivity AE occurs during infusion of amatuximab, the rate of infusion should be decreased by at least 50% and then advanced back (up to a maximum of 10 mg/min). Otherwise, the infusion should be terminated completely in accordance with standard practice at the investigational site or based on the NCI CTCAE v.4.03 (Appendix 1).

In the event of a hypersensitivity AE, the subject may be treated with an additional 650 mg of acetaminophen by mouth, either alone or in combination with diphenhydramine 25 mg to 50 mg by mouth (Grade 1 reaction) or IV (Grade 2 reaction). At any point at which the

investigator deems necessary, other therapeutic interventions should be initiated based on the signs and symptoms and the severity associated with the event.

Secondary Prophylaxis of Hypersensitivity AEs

For subjects who have experienced hypersensitivity AEs, secondary prophylaxis is recommended and given at the investigator's discretion. Details of secondary prophylaxis are outlined in Section 9.3.7.1.1 and below:

- Subjects experiencing hypersensitivity AEs consisting of Grade 1 events can be managed with secondary prophylaxis for subsequent infusions. Along with an antipyretic of choice (acetaminophen to a dose of 1000 mg by mouth has been used) and concurrent use of diphenhydramine, an H2 receptor antagonist can be considered, such as ranitidine (50 mg IV). Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with amatuximab.
- Subjects experiencing hypersensitivity AEs consisting of Grade 2 events can be managed with secondary prophylaxis for subsequent infusions, along with diphenhydramine 50 mg IV, ranitidine 50 mg IV, and dexamethasone 20 mg IV Secondary prophylaxis should be administered approximately 30-60 minutes prior to dosing with amatuximab.

Prophylaxis regimens are given at the investigator's discretion.

If a Grade 3 hypersensitivity AE occurs, the subject may be continued at the discretion of the investigator, provided the reaction can be reduced to and maintained at Grade 2 or lower. In the event that a Grade 4 hypersensitivity AE occurs, the subject will be discontinued from treatment with amatuximab and the study.

Interstitial Lung Disease

Interstitial lung disease AEs are defined as AEs identified in the narrow-search Standardized MedDRA Query for interstitial lung disease (Appendix 2). These events have been seen in clinical studies with other monoclonal antibodies; therefore, they will be monitored in this study and reported to the Sponsor if the meet the criteria of SAEs (see Section 9.4.1.4.2).

Pregnancy Testing

Serum pregnancy testing (β-hCG) was conducted at Screening in female subjects of childbearing potential.

9.4.1.4.4 LABORATORY MEASUREMENTS

Per this amendment, clinical laboratory tests during the Combination Treatment and Maintenance Treatment phases will be performed at the discretion of the PI per standard of care practice by the local laboratory and results will not be collected by the Sponsor.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.4.1.4.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded in the subject's medical records. The corresponding local laboratory values and local lab normal ranges will not be collected.

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.4.1.4.2), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Section 9.4.3.1).

9.4.1.4.5 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs will not be collected during this study due to the absence of clinically significant vital sign findings in prior studies. Any AEs noted as a result of measuring a subject's vital signs as part of standard of care should be recorded in the subject's medical record.

Body weight will be measured at the time points specified in the Schedule of Procedures/Assessments. If weight increases or decreases by more than 10% compared with either Screening or Day 1 of the previous cycle, the amatuximab dosage will be recalculated to maintain the specified dose regimen.

9.4.1.4.6 PHYSICAL EXAMINATIONS

Sites will continue to perform physical examinations at the discretion of the PI per standard of care practice. Documentation of any physical examination will be included in the source documentation at the site.

For postbaseline time points, only body systems where findings are reported as abnormal will be identified, and the associated AE will be reported in the subject's medical record. Abnormal changes from baseline that meet the definition of a SAE should be reported as described in Section 9.4.3.1.

9.4.1.4.7 ELECTROCARDIOGRAMS

Per this amendment, additional ECGs are not required but may be performed at the discretion of the PI.

For ECG abnormalities meeting criteria of an SAE (see Section 9.4.1.4.2), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Section 9.4.3.1).

9.4.2 Schedule of Procedures/Assessments

9.4.2.1 Schedule of Procedures/Assessments

Table 3 presents the Schedule of Procedures/Assessments associated with this amendment.

Table 3 Schedule of Procedures/Assessments in Study MORAb-009-201

Evaluation[a]	Combination Treatment Phase[b]			Maintenance Treatment Phase			Test Article (Amatuximab) Admin Only Visits	EOT Visit[a]	30-Day Safety Visit[c]
	Week 1	Week 2	Week 3	Week 1	Week 2	Week 3			
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15			
ICF[d]									
Physical examination[e]									
Weight[f]	X			X					
Imaging (CT or MRI)[g]									
12-lead ECG[h]									
Hematology and Chemistry[i]									
Premedication (required)[j]	X	X	X	X	X	X	X		
Amatuximab administration[k]	X	X	X	X	X	X	X		
Chemotherapy administration[l]	X								
Concomitant medications[m]	X	X	X	X	X	X	X	X	X
Adverse events[n]	X	X	X	X	X	X	X	X	X

BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; EOT = End of Treatment; ICF = informed consent form; MRI = magnetic resonance imaging

a. All assessments should be performed within ±2 days of the scheduled visit, unless otherwise specified in the protocol, except for EOT Visit assessments, which are to be conducted (where possible) within 7 days of the last dose of Amatuximab. All assessments should be documented in the subject's medical records but will not be collected by the Sponsor. Only SAEs, amatuximab inventory information, and subject discontinuation will be collected per this amendment.
b. All subjects will receive combination treatment for six 21-day cycles. On Day 1 of each cycle, Amatuximab will be administered prior to pemetrexed which will be administered prior to cisplatin. Subjects who have completed a minimum of 4 cycles of Combination Treatment and who have not progressed may enter the Maintenance Treatment Phase.
c. A 30 day Follow-up visit will be performed (within ±7 days) after the last dose of amatuximab and will serve as the last time point for which adverse events are documented in the subject's medical record and SAEs are to be reported.
d. Subjects continuing on study for Amendment 02 should be reconsented to the IRB-approved ICF.
e. Physical examinations should be conducted at the discretion of the investigator per standard of care.
f. Body weight will be measured during Day 1 of each cycle and is entered in the IRT system.
g. CT or MRI scans should conducted at the discretion of the investigator per standard of care.
h. 12-lead ECG should conducted at the discretion of the investigator per standard of care.
i. Hematology and Chemistry should conducted at the discretion of the investigator per standard of care
j. All subjects must be premedicated approximately 30 to 60 minutes prior to each infusion of amatuximab with acetaminophen 650 mg by mouth and diphenhydramine 25 mg to 50 mg by mouth or IV, or clinical equivalent per clinic routine and country availability. Starting at least 5 days prior to the first dose of pemetrexed, subjects will begin treatment with folic acid and vitamin B12. Dexamethasone will be administered at a dose of 4 mg by mouth twice daily for 3 days as follows: the day before, the day of, and the day following each infusion of pemetrexed.
k. Amatuximab must be administered IV once weekly prior to pemetrexed during the Combination Treatment Phase and IV once weekly during the Maintenance Treatment Phase.
l. Pemetrexed will be given prior to cisplatin.
m. Concomitant medications are any new, discontinued, or ongoing medications that have been taken within 30 days prior to the first dose of amatuximab until 30 days after the last dose of amatuximab. These should be discussed and documented in the subject's medical record to assist in identification of AEs.
n. All AEs occurring after the subject signs the ICF and continuing through 30 days after the last infusion of amatuximab should be recorded in the subject’s medical record. Serious AEs should be reported in an expedited fashion per standard procedure. Serious AEs that are ongoing at the time of discontinuation of amatuximab will be followed until resolution (or until stable if resolution is not expected).

9.4.2.2 Description of Procedures/Assessments Schedule

Refer to the Schedule of Procedures/Assessments for details regarding the procedures and assessments required for this study.

9.4.3 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.4.3.1 Reporting of Serious Adverse Events

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

Reporting deaths due to PD as SAEs is not required, as death associated with disease progression.

SAEs, regardless of causality assessment, must be collected from the date of informed consent signature through 30 days following the last dose of amatuximab. SAEs that are ongoing at the time of discontinuation of amatuximab will be followed until resolution (or until stable if resolution is not expected).

Any SAE judged by the investigator to be related to amatuximab 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 call: PPD **(24/7 number)**.

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 24 hours 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 CRO monitor to be filed in the sponsor's Trial Master File (TMF).

9.4.3.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the end of treatment (EOT) Visit of the study and for 30 days following amatuximab discontinuation, whichever is longer, 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 amatuximab.

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 (see Reporting of Serious Adverse Events [Section 9.4.3.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours 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 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.4.3.3 Reporting of Other Events of Interest

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

AEs 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 in the subject's medical record and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.4.3.1) 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.

9.4.3.4 Expedited Reporting

The sponsor must inform investigators 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.

9.4.3.5 Breaking the Blind

The study has been unblinded.

9.4.3.6 Regulatory Reporting of Adverse Events

SAEs 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 SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.4.4 Completion/Discontinuation of Subjects from Study (EOS)

Once a subject discontinues amatuximab for any reason, the EOT procedures should be completed and documented in the subject's medical record.

The investigator will promptly explain to the subject involved that all study procedures 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 presence or absence of AEs, and clinical courses of signs and symptoms.

9.4.5 Abuse or Diversion of Study Drug

Not applicable.

9.4.6 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.

9.5 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.

Before any subjects could be enrolled at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel was conducted. The investigator and all relevant investigational site staff were trained on all aspects of the trial for which they are responsible. Site personnel were trained at a formal initiation visit, and ongoing training will be provided, as necessary.

Monitoring visits will occur at regular intervals while subjects are actively enrolled into the clinical trial. Through frequent communications with the investigational site, the CRA will ensure that the investigation is conducted according to protocol design and all applicable regulatory requirements. Additional details on the monitoring of this clinical trial are provided in Section 11.3.

During the course of the clinical trial, investigational sites and all associated clinical trial documentation may be subject to quality assurance audits by the sponsor, or their appointed representatives, on a planned or an as-needed basis. In addition, representatives of associated regulatory bodies may conduct inspections at their discretion. The investigator is responsible for insuring direct access to all study-related materials for the purpose of these activities.

9.5.1 Data Collection

Per this amendment data-related study information including AEs, results of any standard of care medical or laboratory assessments and information related to amatuximab treatment and drug accountability will be documented in the subject's medical records.

Amatuximab infusion and inventory data, and the date of treatment discontinuation will be entered in the IRT system. SAEs will be reported as outlined in Section 9.4.3.1.

At the beginning of the study, an investigator's study file was established at the investigational site. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP and US 21 CFR Part 312 and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

9.5.2 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.

9.6 Statistical Methods

No efficacy analyses will be performed. Statistical analyses for all other data will be performed by the sponsor or designee on data collected prior to this amendment after the database is locked. Statistical analyses will be performed using SAS® or other validated statistical software as required.

9.6.1 Statistical and Analytical Plans

No formal statistical analyses of efficacy data will be performed. Data collected in the clinical database prior to this amendment will be summarized and listed, as appropriate, in an abbreviated final study report. The specific analysis methods will be described in a separate analysis plan.

9.6.1.1 Safety Analyses

Up until the time of enrollment closure, the IDMC performed periodic safety analyses as detailed in the IDMC charter. No new safety issues were noted.

All safety information entered in the clinical database prior to this amendment will be summarized and included in listings.

Per this amendment, safety information including adverse events should continue to be collected by the investigator and documented in subject's medical record. SAEs must be reported as outlined in Section 9.4.3.1.

9.6.2 Determination of Sample Size

Not applicable.

9.6.3 Interim Analysis for Futility

Not applicable.

9.6.3.1 Independent Data Monitoring Committee

The IDMC will no longer review safety data as the study has been unblinded.

9.6.3.2 Interim Analysis for Futility Assessments

Not applicable.

9.6.4 Other Statistical/Analytical Issues

Not applicable.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Protocols will be followed as written. 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 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 (or if regionally required, the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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).

In general, protocol violations include deviations from inclusion/exclusion criteria, from concomitant medication restrictions, and from any other protocol requirement that could, at least hypothetically, result in significant risk to the subject and/or affect the outcome of the clinical trial. Protocol violations will be noted in the final Clinical Study Report.

A deviation is defined as nonadherence to the protocol procedures or schedule as defined by the protocol or the primary endpoint that does not place the subject at any added or significant risk or affect the data quality or the outcome of the clinical trial (eg, a missed procedure, an out-of-window site visit).

Only subjects who meet protocol-defined eligibility criteria may be enrolled in this clinical trial. If any protocol eligibility criteria or procedures are unclear, the investigator or investigational site personnel should contact the CRA. If the question requires medical interpretation, the sponsor's medical monitor should be consulted. All protocol violations and deviations should be reported to the IRB/IEC according to the standard practices of the investigational site and applicable regulatory requirements.

Data review will be performed in an ongoing manner during trial conduct to assess protocol deviations and violations. The sponsor will convene a data review meeting at least once prior to database lock to classify findings as either protocol deviations or violations.

11.3 Monitoring Procedures

The sponsor's and/or 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 CRAs, as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with ICH GCP and local regulatory requirements. The subject's 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 to 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 that have been certified for accuracy after production
- Recorded data from automated instruments such as IRT, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalograms, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, QOL, 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

The CRA will perform onsite monitoring visit at each site at regular intervals, as agreed upon with the sponsor. At these interim monitoring visits, the CRA (or unblinded CRA, where noted) will perform the following tasks:

- Review data entered into the subject's source documents
- Check for protocol compliance (including documentation of adequate written informed consent, appropriate subject visit dates, documentation of AEs and concomitant medications, key safety and biological safety observations, and study agent dosing)
- Review the investigational site regulatory file to ensure that all regulatory documentation has been updated as necessary and filed appropriately, and reconcile the contents of the investigational site regulatory file the TMF
- Review amatuximab accountability and verify compliance with the Pharmacy Manual

After the last subject at the site has completed the clinical trial, the CRA will return to the site for final source data verification and close-out visit. At this visit, any outstanding issues will be resolved and the investigator's responsibilities for retention of clinical trial documentation will be reviewed.

After each investigational site visit, the CRA will discuss relevant findings with the investigator and the coordinator. The results of the monitoring visit will be documented in a monitoring visit report, and a follow-up letter will be sent to the site.

11.4 Recording of Data

All data associated with conduct of this amendment will be documented in the subject's medical record.

Amatuximab infusion and inventory data, and the date of treatment discontinuation will be entered in the IRT system.

11.5 Identification of Source Data

All data from any safety assessments must be reflected in the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, 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 and as required per local regulations, 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 in the event that the investigator retires or relocates during the retention period, the investigator contacts the sponsor to provide the location where the records are archived, including contact information for the responsible party(ies). This will allow the sponsor to assist in arranging for permanent archiving of the study records.

11.7 Auditing Procedures and Inspection

In addition to 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 Amatuximab

All drug supplies are to be used only for this study and not for any other purpose. All amatuximab will be supplied to the unblinded pharmacist (or qualified designee, as appropriate) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked) in its original packaging, and stored according to the conditions specified on the label. The pharmacist (or qualified designee, as appropriate) must maintain accurate records of amatuximab delivery to the investigational site, inventory at the site, use for each subject, and amatuximab destruction or return. Throughout the study, partially-used and empty vials, as well as any investigational product deemed unusable (eg, as a result of a temperature excursion) must be accounted for.

On close-out of the site, all remaining used vials and unused vials may be destroyed onsite, according to the investigational site's local destruction policy/standard operating procedures, following review of drug accountability records by the unblinded site monitor. The investigational product may also be returned to the sponsor's designated location if previously arranged with the sponsor. The sponsor will assure that a final report of drug accountability to the vial level is prepared and maintained by the investigational site.

A Drug Dispensing Log will be supplied by the sponsor. This log must be kept current and should contain the following information:

- Initial and subsequent inventory on receipt of amatuximab at the investigational site
- Identification (subject number and initials) of each subject to whom the amatuximab was dispensed
- Number of vials of amatuximab used at each visit per subject
- Dates and lot numbers of all amatuximab dispensed
- Number and lot numbers of amatuximab vials destroyed
- Number and lot numbers of amatuximab vials returned

All records and inventory must be available for inspection by the sponsor or its designee (ie, the unblinded CRA), the IRB/IEC, and the relevant regulatory agencies.

Additional details on the storage, handling and inventory of amatuximab will be provided in the Pharmacy Manual.

11.9 Publication of Results

As no formal analyses will be performed there are no planned publications of the results.

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.

The study will be listed on www.clinicaltrials.gov and other registries, as appropriate.

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. The terms of insurance will be kept in the regulatory files.

12 APPENDICES

Appendix 1 National Cancer Institute Common Terminology Criteria for Hypersensitivity Adverse Events

NCI CTCAE CATEGORY[a] Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
IMMUNE SYSTEM DISORDERS					
Allergic reaction Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

NCI CTCAE CATEGORY[a] Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Serum sickness Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately 6 to21 days following the administration of the foreign antigen. Symptoms include fever, arthralgia, myalgia, skin eruption, lymphadenopathy, chest marked discomfort and dyspnea.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L) Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.	38.0–39.0°C (100.4–102.2°F)	>39.0–40.0°C (102.3–104.0°F)	>40.0°C (>104.0°F) for ≤24 h	>40.0°C (>104.0°F) for >24 h	Death

NCI CTCAE CATEGORY[a] **Adverse Event**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chills Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	—	—
Infusion related reaction Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Infusion site extravasation Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.	—	Erythema with associated symptoms (eg, edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

NCI CTCAE CATEGORY[a] Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SKIN AND SUBCUTANEOUS DISORDERS					
Pruritus Definition: A disorder characterized by an intense itching sensation.	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living (ADL)	Intense or widespread; constant; limiting selfcare ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	—	—
Urticaria Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10–30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	—	—
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
Adult Respiratory Distress Syndrome Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.	—	—	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death

NCI CTCAE CATEGORY[a] Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Bronchospasm Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self-care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Dyspnea Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting selfcare ADL	Life-threatening consequences; urgent intervention indicated	Death
Laryngeal edema Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (eg, dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (eg, tracheotomy or intubation)	Death

ADL = activities of daily living; NSAIDS = nonsteroidal antiinflammatory drugs; IV = intravenous.

a) The full NCI CTCAE v4.03 is available at the following web site: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 2 Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms and Codes for Interstitial Lung Diseases Standardized MedDRA Query

MedDRA Preferred Term	MedDRA Code
Acute interstitial pneumonitis	10066728
Allergic granulomatous angitis	10048594
Alveoloar proteinosis	10001881
Alveolitis	10001889
Alveolitis allergic	10001890
Alveolitis fibrosing	10001892
Alveolitis necrotizing	10050343
Bronchiolitis	10006448
Diffuse alveolar damage	10060902
Eosinophilia myalgia syndrome	10014952
Eosinophilic pneumonia	10014962
Eosinophilic pneumonia acute	10052832
Eosinophilic pneumonia chronic	10052833
Idiopathic pneumonia syndrome	10063725
Idiopathic pulmonary fibrosis	10021240
Interstitial lung disease	10022611
Lung infiltration	10025102
Necrotising bronchiolitis	10070831
Obliterative bronchiolitis	10029888
Pneumonitis	10035742
Progressive massive fibrosis	10036805
Pulmonary fibrosis	10037383
Pulmonary necrosis	10058824
Pulmonary radiation injury	10061473
Pulmonary toxicity	10061924
Pulmonary vasculitis	10037457
Radiation alveolitis	10037754
Radiation fibrosis – lung	10037758
Radiation pneumonitis	10037765
Transfusion-related acute lung injury	10052235

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	MORAb-009-201
Study Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination with Pemetrexed and Cisplatin in Subjects with Unresectable Malignant Pleural Mesothelioma
Investigational Product Name:	Amatuximab (MORAb-009)
IND Number:	12894
EudraCT Number:	2014-004489-85

SIGNATURES

Authors:

PPD

30 Jan 2017
Date

Morphotek, Inc.

PPD

30JAN2017
Date

Morphotek, Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	MORAb-009-201
Study Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Amatuximab in Combination with Pemetrexed and Cisplatin in Subjects with Unresectable Malignant Pleural Mesothelioma
Investigational Product Name:	Amatuximab (MORAb-009)
IND Number:	12894
EudraCT Number:	2014-004489-85

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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date