1 TITLE PAGE

STATISTICAL ANALYSIS PLAN

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 (MPM)
Date:	15 October 2019
Version:	Version 1.0

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AEI	adverse event of interest
BSA	body surface area
CRF	case report form
CTCAE	common terminology criteria for adverse events
ECOG	eastern cooperative oncology group
eCRF	electronic case report form
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IRT	interactive response technology (web or voice randomization system)
MPM	malignant pleural mesothelioma
MedDRA	medical dictionary for regulatory activities
Mg/kg	milligram/ kilogram
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	système international
SOC	system organ class
PD	progression
PI	principal investigator
PT	preferred term
Q1	first quartile

Abbreviation	Term
Q3	third quartile
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TLG	tables, listings, and graphs
WHO DD	world health organization drug dictionary

4 INTRODUCTION

The Eisai Protocol MORAb-009-201 is a randomized, double-blind, placebo-controlled phase 2 study of the safety and efficacy of amatuximab in combination with pemetrexed and cisplatin in subjects with unresectable malignant pleural mesothelioma (MPM).

Per Protocol Amendment 02, a business decision was made to discontinue further enrollment in the study as of January 11, 2017 and significantly amended the original protocol to discontinue all ongoing study procedures and conduct, but provided 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 Protocol Amendment 02, only core information necessary for safety monitoring and reporting (i.e., serious adverse event and subject discontinuation data) will be collected. Subjects randomized to placebo and who were in follow-up have been discontinued from the study.

This statistical analysis plan (SAP) follows Protocol Amendment 02 and describes the procedures and the statistical methods that will be used to analyze the safety data and report the safety results for Eisai Protocol MORAb-009-201 (Amendment 02).

4.1 Study Objectives

4.1.1 Primary Objectives

The primary objective 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.

4.1.2 Secondary Objectives

The secondary objective is to monitor safety of ongoing subjects through the collection of serious adverse events (SAEs).

4.2 Overall Study Design and Plan

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 Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1).

Subjects who qualified were randomized to 2 treatment groups: either amatuximab or placebo 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 (i.e., 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 (i.e., Follow-up Phase).

Eisai made a business decision to discontinue any further enrollment in the study as of 11 Jan 2017 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 SAEs and subject discontinuation data will be collected by the Sponsor.
- Subjects will not be followed for efficacy.

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.

5 DETERMINATION OF SAMPLE SIZE

Not Applicable.

6 STATISTICAL METHODS

No efficacy analyses will be performed. Statistical analyses for non-efficacy data will be limited to data collected prior to the date of 22 June 2017. All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, Q1, Q3, minimum and maximum, otherwise will be specified. Categorical variables will be summarized as number (percent) of subjects.

6.1 Study Endpoints

6.1.1 Safety Endpoints

The study endpoints are safety endpoints, which include all AEs, adverse events of interest (AEIs: hypersensitivity AEs and interstitial lung disease AEs), SAEs, clinical laboratory parameters.

6.2 Study Subjects

6.2.1 Definitions of Analysis Sets

The following analysis sets will be defined:

Full Analysis Set includes all randomized subjects according to the treatment assigned by the IRT.
Safety Analysis Set is defined as all randomized subjects who received at least 1 dose of Test Article. Treatment assignments will be designated according to the actual study treatment received. This is the primary analysis population for safety evaluation.

Two additional safety analysis subpopulations will also be defined:

- Combination Treatment Analysis Set consists of subjects in the Safety Analysis Set with any exposure to the study drug of test article in combination with chemotherapy during the combination treatment phase;
- Maintenance Treatment Analysis Set consists of subjects in the Safety Analysis Set with any exposure to the study drug during the maintenance treatment phase.

6.2.2 Subject Disposition

The number of randomized subjects in Full Analysis Set will be summarized by region, country and site. The number of subjects who have been randomized, have received at least 1 dose of Test Article also will be summarized by the study stage and treatment phase; i.e., Combination Treatment phase as well as Maintenance Treatment phase. The number of subjects that discontinue either treatment with Test Article or study will be summarized, along with the reasons for discontinuation.

Per protocol amendment 2 in section 9.2.3, the investigator will discontinue a subject's study treatment (chemotherapies and/or amatuximab) or withdraw the subject from the study if 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. If the last dose date of amatuximab +21 days< cutoff date 22 June 2017 for subjects with no end of treatment and end of study records available, this means they delayed next treatment more than 21

days. These subjects will be treated as discontinued treatment based on test article held greater than 21 days. The discontinuation status of study will be other.

6.2.3 Protocol Deviations

Not applicable.

6.2.4 Demographic and Other Baseline Characteristics

A summary table with descriptive statistics will be generated for demographic s, baseline characteristics, disease characteristics, and disease history, by treatment group for Safety Analysis Set.

Continuous demographic variables include age (year), weight (kg), height (cm) and Body Surface Area (BSA, m^2). Categorical demographic/baseline variables includes age group, gender, race, ethnicity, reproductive status, geographic region, ECOG performance status and pregnancy status. These categorical variables will be summarized based on the categories recorded in the case report form (CRF), except age will be grouped based on the following categories.

Age

- <65 years
- ≥65 to 84 years
- ≥85 years

Other baseline characteristics include the following variables: time from initial diagnosis to randomization (years), age at initial diagnosis (years), stage at initial diagnosis, tumor at initial diagnosis, lymph node at initial diagnosis, metastases at initial diagnosis and histopathology of the tumor (Epithelioid).

Subject listing of demographics and baseline characteristics including sex, race, ethnicity, body weight, height, BSA, reproductive status and analysis set information will be presented.

A summary table of medical history/current medical condition by system organ class and preferred term by treatment group and overall will be provided.

6.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded using the World Health Organization Drug Dictionary (WHO DD) version of WHODDMAR16B2.

Premedications are defined as medications prior to infusion per Protocol. All subjects must be premedicated prior to each infusion of amatuximab and the first dose of pemetrexed.

Concomitant medications are defined as 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.

A subject data listing of prior and concomitant medications including premedications and concomitant medications will be provided.

6.3 Data Analysis General Considerations

6.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses. Center will not be considered as a factor in the analysis.

6.3.2 Adjustments for Covariates

Not applicable.

6.3.3 Multiple Comparisons/Multiplicity

Not applicable.

6.3.4 Examination of Subgroups

Not applicable.

6.3.5 Handling of Missing Data, Drop-outs, and Outliers

Adverse Events with incomplete start dates will be considered treatment emergent if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;
b. Day is missing, and the year is after the year of the first dose;
c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;
d. Year is missing; or
e. Complete date is missing.

Medications will be considered concomitant if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;
b. Day is missing, and the year is after the year of the first dose;
c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or

d. Year is missing; or
e. Complete date is missing.

If there is no treatment or study discontinuation records from disposition page on eCRF, and the days between date of last actual dose of amatuximab and the date of 22 June 2017 were greater than 21 days for the subject, the information of last exposure of Amatuximab for those subjects was imputed as follows:

Planned dose is 0 mg, actual dose is 0 mg for the imputed last dose of Amatuximab and the imputed start/end date of last dose is the start/end date of last actual dose +21 days, duration of exposure will be based on the imputed last dose end date.

The imputation rules will be specified in study analysis dataset specification with more details.

6.4 Efficacy Analyses

Not applicable.

6.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic and Other Biomarker Analyses

Not applicable.

6.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized by treatment group using descriptive statistics (i.e., n, mean, SD, median, Q1, Q3, minimum and maximum for continuous variables; and n (%) for categorical variables). Safety variables include extent of exposure to study drugs, Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Adverse Events (TRAEs), clinical laboratory parameters.

Study Day 1 for all safety analyses will be defined as the date of the first dose of any study drug administrated.

6.6.1 Extent of Exposure

The administration profile of Test Article (amatuximab 5 mg/kg or placebo) will be summarized with respect to the number of cycles/infusions of treatment in the Overall study as well as summarized by Combination Treatment phase and Maintenance Treatment phase.

Duration of exposure in weeks ([(date of last test article infusion – date of first test article infusion) + 1] / 7), total dose (mg/kg), actual dose intensity (mg/kg/week), and relative dose

intensity (actual dose intensity divided by the planned dose intensity) will be summarized for Test Article by treatment group for the Safety Analysis Set with descriptive statistics.

Exposure summaries will be reported for each chemotherapy (Pemetrexed and Cisplatin regimen).

The information of last exposure of test article was imputed for subjects with no end of treatment/study records and last actual dose of test article were held greater than 21 days, see Section 6.3.5 for data handlings.

Administration Records of Test article, Pemetrexed and Cisplatin regimen will be listed.

6.6.2 Adverse Events

The adverse event verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA. The severity of the toxicities will be graded according to the NCI CTCAE v4.03, where applicable.

All AEs, regardless of relationship to study drug or procedure, must be followed for 30 days after the subject's last dose of test article, or until resolution, whichever comes first per protocol.

All AEs occurred from the earliest date of first dose of study drugs to 30 days after the latest date of last dose of study drugs were included in TEAEs and TRAEs analysis.

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

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

A TRAE is defined as a TEAE that was classified by the investigator as related to treatment with Test Article.

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

All the TEAEs and TRAEs tables will be summarized by treatment group and by Combination Treatment phase versus Maintenance Treatment phase based on Safety Analysis Set.

TEAEs will be "slotted" to a treatment phase (ie, combination treatment versus maintenance treatment) based on their onset date and applying the rules for "Phases" in Section 10.

An overview table, including the incidence (percentage) of subjects with TEAEs, test article-related and chemotherapy-related TEAEs with grade 3 or higher, SAEs and test article-related SAEs, TEAEs with Maximum grade(1-4), TEAEs leading to action taken with Test Article and chemotherapy, deaths and TEAEs that led to treatment discontinuation and drug interruption/delay (of test article) will be provided by treatment group.

The incidence of TEAEs and TRAEs will be reported as the number of occurrences and the number (percentage) of subjects with TEAEs or TRAEs by SOC and PT. Occurrences of each event are calculated as follows: Count each event once unless two AEs with the same preferred term occur on the same day. If two events occur on the same day and the start and stop times indicate that they are separate events then count both. Otherwise, if the severity and relationship of both events are the same then count them as one occurrence, if the severity or relationship of both events are different, count them as separate occurrences.

For the number (percentage) of subjects count, subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE or TRAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs or TRAEs will also be summarized by their highest CTCAE grade.

In summary, the following TEAE tables will be provided:

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term;
- Treatment- Emergent Adverse Events by System Organ Class, Preferred Term, and Worst CTCAE Grade (including any grade 1, 2, ≥3, 3, 4 and 5)
- Treatment-Emergent Adverse Events with CTCAE Grade ≥3 by System Organ Class and Preferred Term
- Test Article-related TEAEs with CTCAE Grade ≥3 by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events ≥ 5% by Preferred Term in Decreasing Frequency
- Test Article-Related Treatment-Emergent Adverse Events ≥ 5% by Preferred Term in Decreasing Frequency

The following subject AE listings will be provided:

- All Adverse Events.

6.6.3 Deaths, Serious and Other Significant Adverse Events

Per protocol, SAEs must be collected from the date of informed consent signature through 30 days following the last dose of amatuximab. Any untoward medical occurrence resulting in death (death due to PD as this is study endpoint) is not counted as serious adverse event.

The number (percentage) of subjects with treatment-emergent SAEs (including Subjects affected/exposed, Occurrences causally related to Treatment /all and Deaths causally related to Treatment/all by test article and chemotherapy separately) and Non-SAEs at 5% threshold will be summarized by treatment group, MedDRA SOC and PT. In addition, Subject data listing of all SAEs and all deaths will be provided.

TEAEs leading to discontinuation of test article by SOC and PT will also be summarized.

6.6.3.1 Adverse Events of Interest

The conditions of hypersensitivity AEs and interstitial lung disease AEs are two possible groups with administration of any monoclonal antibody and should be considered as AEIs. The AEIs will be classified into hypersensitivity and interstitial lung disease groups of preferred terms.

Hypersensitivity

A hypersensitivity AE is defined as a TEAE occurring within 2 days of infusion to Test Article from a pre-defined list of AE terms. An abbreviated NCI CTCAE v.4.03 for grading some of the most commonly observed hypersensitivity AEs has been provided (Section 14.1). Refer to the full NCI CTCAE v.4.03 for complete event grading information. 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

In order for an AE to be classified as hypersensitivity AE, the following criteria are simultaneously required:

1. The AE term must meet a pre-identified MedDRA term in a pre-defined group search basket for hypersensitivity AEs.
2. The AE term must be a TEAE.
3. The AE must follow the 2-day rule; that is, the AE must have an onset date occurring the same day or the day after exposure to Test Article.

A separate excel spreadsheet containing a group search PT terms for hypersensitivity will be used to identify hypersensitivity AEs.

Interstitial Lung Disease

Interstitial lung disease (ILD) AEs are defined as AEs identified in the narrow-search Standardized MedDRA Query for interstitial lung disease (Section 14.2), ILD AEs will include, but not limited to the following terms:

- Interstitial lung disease
- Pulmonary fibrosis
- Pneumonitis

The following AEIs information will be summarized by overall study and treatment phase, otherwise specified.

- Overall AEIs (Adverse event of interest) by SOC and PT (hypersensitivity and ILD) Safety Analysis Set
- Overview of AEIs for Interstitial Lung Disease Safety Analysis Set (if there is no events, then no table)

6.6.4 Laboratory Values

Hematological and chemistry laboratory findings will be graded according to NCI CTCAE v.4.03, where applicable.

Actual values and change from baseline for laboratory parameters will be summarized by treatment group and visit using descriptive statistics.

All laboratory data will be presented in data listings.

6.7 Exploratory Analyses

Not applicable.

7 INTERIM ANALYSES

Not applicable.

8 CHANGES IN THE PLANNED ANALYSES

Not applicable.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications will be provided in separate documents.

10 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Study Day 1

Study Day 1 for all safety analyses will be defined as the date of the first dose of any study drug administrated.

Baseline

Baseline is defined as the last non-missing assessment prior to the first dose of any study drug administrated.

Phase Rule

- Combination Treatment Phase: any collection date < the date of the first maintenance treatment;
- Maintenance Treatment Phase: any collection date ≥ the date of the first maintenance treatment.

By-visit analyses

All by-visit analyses will be performed using assessments at corresponding scheduled visits recorded in the eCRF.

Incomplete dates

For incomplete dates involving safety data, see Section 6.3.5 for data handlings.

11 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9 or higher, and/or other validated statistical software as required.

12 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

13 REFERENCES

1. Study Protocol Number: MORAb-009-201: 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 (v3.0V1.0 – 30 Jan 2017).
2. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, May 28, 2009.
3. FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

14 APPENDICES

14.1 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
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	Asymptomatic; clinical or diagnostic	Moderate arthralgia; fever, rash, urticaria, antihistamines	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids	Life-threatening consequences;	Death

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.	observations only; intervention not indicated	indicated	indicated	pressor or ventilatory support indicated	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 109/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)	>40.04 C (>104.0°F) for ≤24 h	>40.0°C (>104.0°F) for >24 h	Death
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,	-	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

burning sensation and marked discomfort at the infusion site.					
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
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	Asymptomatic; clinical or	Symptomatic; medical intervention indicated	Stridor; respiratory distress; hospitalization	Life-threatening	Death

characterized by swelling due to an excessive accumulation of fluid in the larynx.	diagnostic observations only; intervention not indicated	(eg, dexamethasone, epinephrine, antihistamines)	indicated	airway compromise; urgent intervention indicated (eg, tracheotomy or intubation)	

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:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.2 Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 Preferred Terms and Codes for Interstitial Lung Diseases Standardized MedDRA Query

MedDRA Preferred Term	MedDRA Code
10066728	Acute interstitial pneumonitis
10073344	Alveolar lung disease
10001881	Alveolar proteinosis
10001889	Alveolitis
10001890	Alveolitis allergic
10050343	Alveolitis necrotising
10006448	Bronchiolitis
10076515	Combined pulmonary fibrosis and emphysema
10060902	Diffuse alveolar damage
10014952	Eosinophilia myalgia syndrome
10078117	Eosinophilic granulomatosis with polyangiitis
10014962	Eosinophilic pneumonia
10052832	Eosinophilic pneumonia acute
10052833	Eosinophilic pneumonia chronic
10078268	Idiopathic interstitial pneumonia
10063725	Idiopathic pneumonia syndrome
10021240	Idiopathic pulmonary fibrosis
10022611	Interstitial lung disease
10025102	Lung infiltration
10070831	Necrotising bronchiolitis
10029888	Obliterative bronchiolitis
10035742	Pneumonitis
10036805	Progressive massive fibrosis
10037383	Pulmonary fibrosis
10058824	Pulmonary necrosis
10061473	Pulmonary radiation injury
10061924	Pulmonary toxicity
10037457	Pulmonary vasculitis
10037754	Radiation alveolitis
10037758	Radiation fibrosis - lung
10037765	Radiation pneumonitis
10052235	Transfusion-related acute lung injury

14.3 Corrected Calcium formula

Corrected Ca (mmol/L) = Ca measured (mmol/L) + 0.025 (40 - albumin (g/L))

The formula is not applicable when serum albumin concentration is normal (>40 g/L); in such situations, the total (uncorrected) serum calcium should be used instead.

14.4 BSA formula

BSA is derived using Dubois formula: BSA (m2) = 0.20247 x Height $(m)^{0.725}$ x Weight $(kg)^{0.425}$

SIGNATURE PAGE

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