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
2 TABLE OF CONTENTS

1 TITLE PAGE ................................................................. 1
2 TABLE OF CONTENTS .................................................. 2
3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS .... 4
4 INTRODUCTION .............................................................. 6
  4.1 Study Objectives ....................................................... 6
    4.1.1 Primary Objectives ............................................. 6
    4.1.2 Secondary Objectives ......................................... 6
  4.2 Overall Study Design and Plan .................................... 6
5 DETERMINATION OF SAMPLE SIZE ......................... 7
6 STATISTICAL METHODS ............................................... 7
  6.1 Study Endpoints ...................................................... 8
    6.1.1 Safety Endpoints ............................................. 8
  6.2 Study Subjects ....................................................... 8
    6.2.1 Definitions of Analysis Sets ................................ 8
    6.2.2 Subject Disposition ......................................... 8
    6.2.3 Protocol Deviations ......................................... 9
    6.2.4 Demographic and Other Baseline Characteristics .... 9
    6.2.5 Prior and Concomitant Therapy ......................... 9
  6.3 Data Analysis General Considerations ..................... 10
    6.3.1 Pooling of Centers .......................................... 10
    6.3.2 Adjustments for Covariates .............................. 10
    6.3.3 Multiple Comparisons/Multiplicity .................... 10
    6.3.4 Examination of Subgroups ............................... 10
    6.3.5 Handling of Missing Data, Drop-outs, and Outliers .. 10
  6.4 Efficacy Analyses ................................................... 11
  6.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic and Other Biomarker Analyses ........................................... 11
  6.6 Safety Analyses ..................................................... 11
    6.6.1 Extent of Exposure ......................................... 11
    6.6.2 Adverse Events ............................................ 12
    6.6.3 Deaths, Serious and Other Significant Adverse Events ... 14
      6.6.3.1 Adverse Events of Interest ........................ 14
    6.6.4 Laboratory Values ......................................... 15
  6.7 Exploratory Analyses .............................................. 15
7 INTERIM ANALYSES .................................................. 16
8 CHANGES IN THE PLANNED ANALYSES ............................................................... 16
9 PROGRAMMING SPECIFICATIONS ................................................................. 16
10 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING .................. 16
11 STATISTICAL SOFTWARE ............................................................................... 16
12 MOCK TABLES, LISTINGS AND GRAPHS (TLGS) .......................................... 17
13 REFERENCES .................................................................................................... 17
14 APPENDICES .................................................................................................. 18
   14.1 National Cancer Institute Common Terminology Criteria for Hypersensitivity
       Adverse Events .................................................................................................. 18
   14.2 Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1
       Preferred Terms and Codes for Interstitial Lung Diseases Standardized
       MedDRA Query ................................................................................................. 22
   14.3 Corrected Calcium formula ........................................................................ 23
   14.4 BSA formula ................................................................................................. 23
### 3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AEI</td>
<td>adverse event of interest</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CTCAE</td>
<td>common terminology criteria for adverse events</td>
</tr>
<tr>
<td>ECOG</td>
<td>eastern cooperative oncology group</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>IDMC</td>
<td>independent data monitoring committee</td>
</tr>
<tr>
<td>ILD</td>
<td>interstitial lung disease</td>
</tr>
<tr>
<td>IRT</td>
<td>interactive response technology (web or voice randomization system)</td>
</tr>
<tr>
<td>MPM</td>
<td>malignant pleural mesothelioma</td>
</tr>
<tr>
<td>MedDRA</td>
<td>medical dictionary for regulatory activities</td>
</tr>
<tr>
<td>Mg/kg</td>
<td>milligram/kilogram</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SI</td>
<td>système international</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>PD</td>
<td>progression</td>
</tr>
<tr>
<td>PI</td>
<td>principal investigator</td>
</tr>
<tr>
<td>PT</td>
<td>preferred term</td>
</tr>
<tr>
<td>Q1</td>
<td>first quartile</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Q3</td>
<td>third quartile</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>TRAE</td>
<td>treatment-related adverse event</td>
</tr>
<tr>
<td>TLG</td>
<td>tables, listings, and graphs</td>
</tr>
<tr>
<td>WHO DD</td>
<td>world health organization drug dictionary</td>
</tr>
</tbody>
</table>
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, m²). 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

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, \(\geq 3\), 3, 4 and 5)
- Treatment-Emergent Adverse Events with CTCAE Grade \(\geq 3\) by System Organ Class and Preferred Term
- Test Article-related TEAEs with CTCAE Grade \(\geq 3\) by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events \(\geq 5\%\) by Preferred Term in Decreasing Frequency
- Test Article-Related Treatment-Emergent Adverse Events \(\geq 5\%\) 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 AEs. The AEs 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

14 APPENDICES

14.1 National Cancer Institute Common Terminology Criteria for Hypersensitivity Adverse Events

<table>
<thead>
<tr>
<th>NCI CTCAE CATEGORY&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNE SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>Transient flushing or rash, drug fever &lt;38 degrees C (&lt;100.4 degrees F); intervention not indicated</td>
<td>Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hrs</td>
<td>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)</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>Mild reaction; infusion interruption not indicated; intervention not indicated</td>
<td>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h</td>
<td>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)</td>
<td>Life-threatening consequences; pressor or ventilatory support indicated</td>
<td>Death</td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Asymptomatic; clinical or diagnostic</td>
<td>Moderate arthralgia; fever, rash, urticaria, antihistamines</td>
<td>Severe arthralgia or arthritis; extensive rash; steroids or IV fluids</td>
<td>Life-threatening consequences;</td>
<td>Death</td>
</tr>
<tr>
<td>Definition: A disorder characterized by a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.
### Delayed-Type Hypersensitivity Reaction to Foreign Proteins

<table>
<thead>
<tr>
<th>Observation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation not indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by elevation of the body's temperature above the upper limit of normal.

### Fever (in the absence of neutropenia, where neutropenia is defined as ANC < 1.0 x 10^9/L)

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>38.0–39.0°C (100.4–102.2°F)</td>
<td>Mild sensation of cold, shivering; chattering of teeth</td>
</tr>
<tr>
<td>&gt;39.0–40.0°C (102.3–104.0°F)</td>
<td>Moderate tremor of the entire body; narcotics indicated</td>
</tr>
<tr>
<td>&gt;40.0°C (&gt;104.0°F) for ≤24 h</td>
<td>Severe or prolonged, not responsive to narcotics</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.

### Chills

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild sensation of cold, shivering; chattering of teeth</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.

### Infusion Related Reaction

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild transient reaction; infusion interruption not indicated; intervention not indicated</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

### Infusion Site Extravasation

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema with associated symptoms (eg, edema, pain, induration, phlebitis)</td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by leakage of a pharmacologic or biological substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling.

### General Disorders and Administration Site Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
</tr>
</tbody>
</table>

**Definition:** A disorder characterized by elevation of the body's temperature above the upper limit of normal.
**SKIN AND SUBCUTANEOUS DISORDERS**

| Condition        | 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**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
<th>Treatment</th>
<th>Severe Complications</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult Respiratory Distress Syndrome</strong></td>
<td>A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.</td>
<td>Present with radiologic findings; intubation not indicated</td>
<td>Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td><strong>Bronchospasm</strong></td>
<td>A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.</td>
<td>Mild symptoms; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Limiting self-care ADL; oxygen saturation decreased</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>A disorder characterized by an uncomfortable sensation of difficulty breathing.</td>
<td>Shortness of breath with moderate exertion</td>
<td>Shortness of breath with minimal exertion; limiting instrumental ADL</td>
<td>Shortness of breath at rest; limiting selfcare ADL</td>
</tr>
<tr>
<td><strong>Laryngeal edema</strong></td>
<td>A disorder</td>
<td>Asymptomatic; clinical or</td>
<td>Symptomatic; medical intervention indicated</td>
<td>Stridor; respiratory distress; hospitalization</td>
</tr>
</tbody>
</table>
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

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