Statistical Analysis Plan I5B-MC-JGDR

A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients With Advanced or Metastatic Soft Tissue Sarcoma

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Approval Date: 28-Aug-2017

1. Statistical Analysis Plan I5B-MC-JGDR: A Phase 1b Study of Olaratumab, Doxorubicin and Ifosfamide in the Treatment of Patients with Advanced or Metastatic Soft Tissue Sarcoma

Olaratumab (LY3012207) Soft Tissue Sarcoma

Study JGDR is a Phase 1b, multicenter, nonrandomized, open-label study of intravenous olaratumab (15 mg/kg on Days 1 and 8 or 20-mg/kg loading dose on Days 1 and 8 in Cycle 1 followed by 15 mg/kg on Days 1 and 8 of subsequent cycles) combined with doxorubicin (25 mg/m^2 on Days 1, 2, 3), ifosfamide (2.5 g/m^2 on Days 1, 2, 3, 4) and mesna (≥60% of ifosfamide dose on Days 1, 2, 3, 4) in 21-day cycles in the treatment of patients with advanced or metastatic soft tissue sarcoma. Patients will receive combination treatment for a maximum of 6 cycles followed by olaratumab as monotherapy until there is evidence of disease progression, death, intolerable toxicity, or other withdrawal criteria are met.

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Protocol I5B-MC-JGDR
Phase 1b

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 28-Aug-2017 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

4. Study Objectives

4.1. Primary Objective

The primary objective is to characterize the safety profile of olaratumab when given in combination with doxorubicin, ifosfamide and mesna and to determine the dosing regimen appropriate for a future Phase 2 study.

4.2. Secondary Objectives

The secondary objectives are:

- to evaluate the pharmacokinetics (PK) of olaratumab when combined with doxorubicin, ifosfamide and mesna
- to evaluate the immunogenicity of olaratumab when combined with doxorubicin, ifosfamide and mesna
- to document any antitumor activity of olaratumab when combined with doxorubicin, ifosfamide and mesna

4.3. Exploratory Objectives

The primary objective is to explore biomarkers related to, but not limited to tumor microenvironment, immune cells/immune functioning, mechanism of action of study drugs, platelet-derived growth factor receptor (PDGF), cancer-related pathways and disease state, and their association with demographics, disease state and clinical outcomes.

5. A Priori Statistical Methods

5.1. Sample Size Determination

The sample size determination is described in Protocol I5B-MC-JGDR (JGDR), Section 10.1.

5.2. General Considerations

5.2.1. Populations

The following population will be defined for this study:

Safety population: All enrolled patients who receive any quantity of study treatment, regardless of their eligibility for the study, will be included in the safety analysis. Safety evaluation will be performed based on the actual initial therapy a patient has received. Efficacy analysis will be performed on the safety population unless otherwise specified.

DLT-evaluable population: The DLT-evaluable population will include all enrolled patients who complete Cycle 1 or discontinue due to a DLT prior to completing Cycle 1.

5.2.2. Definitions and Conventions

The **baseline value** is the last non-missing value observed prior to the first dose of study treatment.

The **study day** will be calculated as: assessment date – first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date.

Date of first dose is defined as study Day 1.

One month is defined as 365/12 days.

Unless otherwise noted, **summaries of continuous variables** will include mean, median, standard deviation, minimum, and maximum. When appropriate, lower and upper quartiles will also be presented.

Unless otherwise noted, summaries of **categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

5.3. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant sections.

5.4. Multiplicity adjustment

Multiplicity will not be adjusted.

5.5. Patient Disposition

The number and percentage of patients entered into the study, treated in the study, as well as reasons for discontinuation from study treatment and reasons for discontinuation from study, will be summarized overall as well as by treatment cohort. A listing of patient disposition will also be provided.

Significant protocol violations that potentially compromise the data integrity and patients' safety will be summarized for safety population. These violations will include deviations that can be identified programmatically and those that can only be identified by the clinical research associate during monitoring. Significant protocol violations are described in the Trial Issue Management Plan within the study Trial Master File.

5.6. Patient Characteristics

5.6.1. Demographics

Patient demographics will be summarized for safety population. Patient demographics will include country, age, sex, race, ethnicity, height, weight, and body surface area (BSA).

5.6.2. Baseline Disease Characteristics

Eastern Cooperative Oncology Group (ECOG) performance status (PS), initial pathological diagnosis, basis for initial diagnosis, disease stage, histopathological grade, TNM stage and time since initial diagnosis will be summarized for safety population using descriptive statistics and listed in a data listing.

5.6.3. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Terms [PT] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA™]) will be summarized.

5.6.4. Prior Therapies

Prior radiotherapy, surgery, systemic and locoregiojnal therapy will be summarized. Prior radiotherapy will be categorized by reason (neoadjuvant, adjuvant, neoadjuvant plus adjuvant, advanced/metastatic) for the regimen and prior surgery will be categorized by intent (curative, palliative). Prior systemic and locoregiojnal therapy will be categorized by treatment intent (curative, palliative) and setting (neoadjuvant, adjuvant, locally advanced, metastatic). Frequency of each specific therapy will be tabulated within each type of regimen and reason for regimen.

5.6.5. Poststudy Treatment Discontinuation Therapies

Therapies received following study treatment discontinuation will be summarized overall and by type of therapy.

5.7. Concomitant Therapy

Concomitant medications including indication for use (primary study condition, AE or medical history event, prophylaxis) will be summarized and listed.

5.8. Safety Analyses

All safety analyses will be performed on the safety population within each cohort. Safety analyses will also be performed combining patients treated within the dose confirmatory phase with patients treated at the same dose level within the dose finding phase.

5.8.1. Extent of Exposure

Drug exposure, dose intensity, drug adjustments (dose omissions, interruptions, reductions) and dose delays for olaratumab, doxorubicin, ifosfamide and mesna will be summarized for all treated patients.

Drug exposure will include the following summaries:

- Number of cycles received per patient
- Duration on therapy: (date of last cycle Day 1 − date of first dose + 21) ÷ 7, [weeks]
- Cumulative dose: sum of dose administered at each infusion per patient per compound, [mg]
- Weekly dose intensity: the actual cumulative amount of drug taken divided by the duration of treatment in weeks
    - Olaratumab: cumulative dose / last available weight / duration of therapy, [mg/kg/week]
    - Doxorubicin: cumulative dose / BSA derived using last available weight / duration of therapy, [mg/m^2/week]
    - Ifosfamide: cumulative dose / BSA derived using last available weight / duration of therapy, [mg/m^2/week]
    - Mesna: cumulative dose / BSA derived using last available weight / duration of therapy, [mg/m^2/week]
- Relative dose intensity: the actual amount of drug taken divided by the amount of drug prescribed times 100%, [%]

The summary of dose adjustments and delays will include the reason for adjustment or delays.

5.8.2. Dose-Limiting Toxicity and DLT-Equivalent Toxicities

The definition and derivation of the dose limiting toxicities (DLT) and the DLT-equivalent toxicities (DET) is specified in Protocol JGDR, Section 7.2.2.

DLT will be summarized and listed for DLT-evaluable population. DET will also be listed and summarized for safety population.

5.8.3. Adverse Events

Adverse event (AE) severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 4. AE verbatim text will be mapped by the sponsor or designee to corresponding terminology within MedDRA.

Pre-existing conditions are defined as any AEs that begin prior to the first dose of study drug.

Treatment-emergent adverse event (TEAE) are defined as any AE that occurred or worsened between the day of first dose and up to 30-day follow-up visit (or up to any time if serious and related to study treatment).

Comparisons of pre-existing conditions to on-treatment events at the low level term (LLT) level will be used in the treatment-emergent computation.

The following AE will be considered as **AE of special interest** (AESI) for the combination of olaratumab and doxorubicin, ifosfamide and mesna: infusion-related reactions (IRR), cardiac arrhythmias, cardiac dysfunction, encephalopathy, renal toxicity. PT for AESI are listed in Appendix 1. Categories of AESI may be modified as the understanding of the safety of the investigational drug increases. The final list of categories will be reported in the clinical study report (CSR).

Consolidated AE will include Abdominal Pain, Anemia, Fatigue, Hyperbilirubinaemia, Hypertension, Hypoalbuminaemia, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Hypoproteinemia, Intestinal Obstruction, Leukocytosis, Leukopenia, Lymphopenia, Mucositis, Neuropathy, neutropenia, Musculoskeletal pain, Rash, and Thrombocytopenia. Each consolidated AE contains PTs identified as clinically identical or synonymous. PT for consolidated AEs are listed in Appendix 2.

The following summaries and listings will be produced:

- Overview of AE
- Summary of TEAE by PT (any grade and Grade ≥ 3)
- Summary of DLT
- Summary of DET
- Summary of TEAE by system organ class (SOC) and PT (any grade and Grade ≥ 3)
- Summary of TEAE by SOC and PT and maximum grade (1-5)
- Summary of treatment-emergent serious AE (SAE) by SOC and PT (any grade and Grade ≥ 3)
- Summary of AEs as reason for study treatment discontinuation by SOC and PT
- Summary of and listing of TEAE leading to dose delays, omissions, interruptions, reductions, treatment discontinuation, hospitalizations, transfusions

- Summary of treatment-emergent AESI (any grade and Grade ≥ 3)
- Summary of treatment-emergent consolidated AE (any grade and Grade ≥ 3)
- Listings of DLT, DET, SAE, TEAE, AESI

The TEAE and SAE summaries will be produced for all TEAE/SAEs and repeated for TEAE/SAE related to study treatment, where relationship of the AE to the study treatment will be assessed by the investigator (yes or no).

5.8.4. Deaths, Other Serious Adverse Events

A summary of all deaths, including reasons for deaths, will be provided. All deaths, deaths on therapy, deaths within 30 days of discontinuation of study therapy, deaths on therapy or within 30 days of discontinuation of study therapy, and deaths after 30 days of discontinuation of study therapy will be summarized by reason for death. For deaths due to AE, the preferred term will be provided. In addition to the tabular summary, a by-patient listing of all deaths on study not attributed to study disease by the investigator will be provided.

5.8.5. Medical History Related to Infusion Related Reactions or Hypersensitivity

Summaries will be provided for prespecified medical history related to IRR or hypersensitivity for a patient and patient's first degree relatives.

5.8.6. Clinical Laboratory Evaluation

All relevant laboratory values will be graded according to CTCAE Version 4. Treatment-emergent changes will be summarized by the maximum postbaseline grade, and a shift table of baseline grade by maximum postbaseline grade will be produced. A listing will be provided with a flag for values outside of the laboratory normal range.

5.8.7. Vital Signs and Other Physical Findings

Actual values and changes from baseline for vital signs including temperature, blood pressure, respiratory and heart rate will be summarized by scheduled time point using descriptive statistics and listed. A summary of ECOG performance status at each scheduled time point will be provided.

5.8.8. Electrocardiograms, Echocardiogram / Multiple Gated Acquisition Scan

Electrocardiograms (ECG) findings that are considered to be a medical history condition or an AE will be summarized and listed.

Left ventricular ejection fraction (LVEF) results will be summsrised by scheduled time point.

Changes in LVEF will also be summarized including percentage of patients with LVEF decrease of ≥10% and below the lower limit of normal, or an absolute decrease of 20%, or an absolute LVEF decreases to or below 40%.

5.9. Efficacy Analyses

All efficacy analyses will be performed on the safety population to investigate antitumor activity within each cohort. This study is not designed to perform hypothesis testing on efficacy.

Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 will be applied as the primary criteria for assessment of tumor response. Local tumor imaging (investigator assessment with site radiological reading) will be used.

All time-to-event variables will be estimated using Kaplan-Meier method (Kaplan and Meier 1958) and summary statistics including median along with 95% CI as well as even-free rates (and 95% CI) at different time points will presented.

5.9.1. Objective Response Rate and Disease Control Rate

Objective response rate (ORR) and disease control rate (DCR) are summary measures of best overall response (BOR) as defined by RECIST. BOR is derived from time point responses. All time point responses observed while on study treatment and during the short-term follow-up period (but before the initiation of postdiscontinuation therapy) will be included in the derivation. Best overall response of complete response (CR) and partial response (PR) should be confirmed by repeated assessment at least 4 weeks following the initial observation. Each patient's BOR will categorized as CR, PR, stable disease (SD), PD, or not evaluable (NE). If appropriate, the best overall tumor response may be derived using all available lesion measurement data to confirm the investigator assessments.

ORR will be estimated by dividing the total number of responders (CR+PR) by the number of treated patients. DCR is defined as the number of patients with SD, confirmed PR or confirmed CR (CR+PR+SD) divided by the number of treated patients. The estimates of ORR and DCR will be reported with exact 95% confidence interval (CI) for each arm.

Individual changes in the tumor burden over time will be presented graphically by waterfall and spier plots within a tumor type.

5.9.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of first dose until the date of radiographic documentation of progression (as defined by RECIST) based on investigator assessment or the date of death due to any cause, whichever is earlier. It is calculated as date of progression / censor – date of first treatment + 1.

Table JGDR.5.1 lists rules for determining date of progression or censor for PFS.

Table JGDR.5.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessment	Date of first dose	Censored
2	No postbaseline assessments and no death	Date of first dose	Censored
3	No documented progression and no death (with a postbaseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive postbaseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of first treatment, whichever is later.	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies. If there are multiple dates associated with 1 radiological tumor assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise. A radiological tumor assessment is considered adequate if its response is among CR, PR, SD, or PD. Symptomatic deteriorations (that is, symptomatic progressions, which are not radiologically confirmed) will not be considered as disease progressions.

5.9.3. Duration of Response

The duration of response (DoR) time is defined only for responders (patients with a confirmed CR or PR). It is measured from the date of first evidence of CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. For clarity, the start date should be determined by the initial assessment of CR or PR, not the date of confirmation of CR or PR. It is calculated as date of progression or death – date of first response evaluation of CR or PR + 1.

Duration of response (DoR) will be censored according to the same rules as PFS, with the addition of the following rule: if a patient begins postdiscontinuation therapy, DoR will be censored on the day of the last response evaluation prior to the initiation of postdiscontinuation therapy.

5.9.4. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose until the date of death due to any cause. If the patient is alive at the cutoff date for the analysis (or was lost to follow-up without a confirmed date of death), OS will be censored on the last date the patient was known to be alive.

5.10. Subgroup Analyses

Subgroup analyses may be performed as deemed appropriate. The following analyses will be considered, depending on the number of patients within each subgroup:

- Safety analyses based on different infusion type of doxorubicin (intravenous route of administration over 60 minutes versus a 24-hour continuous infusion).
- Safety analyses related to cardiac toxicity based on subgroup of patients received dexrazoxane.
- Safety analyses related to urotoxicity based on different mesna dose levels.

5.11. Pharmacokinetics and Immunogenicity

A separate analysis plan will be provided for PK and immunogenicity analyses.

5.12. Biomarker Analysis

The detailed biomarker analysis will be included in a separate biomarker analysis plan.

5.13. Development Safety Update Report

The following reports are needed for the Development Safety Update Report (DSUR):

- Exposure information
- Listing of subjects who died during the DSUR period
- Discontinuations due to AEs during the DSUR Period

5.14. Clinical Trial Registry

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized by treatment group and by MedDRA Preferred Term.
- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious.
- For each SAE and "Other" AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event (if certain subjects cannot be at risk for some reason, for example, gender-specific AEs, then the number will be adjusted to only include the patients at risk)
    - the number of participants who experienced each event term
    - the number of events experienced.

- For each SAE, for each term and treatment group, the following are also provided for the EudraCT results submission:
    - The number of occurrences (events) causally related to treatment
    - The total number of deaths
    - The number of deaths causally related to treatment
- Consistent with www.ClinicalTrials.gov requirements, a threshold for frequency of "Other" AEs can be implemented rather than presenting all "Other" AEs. For example, "Other" AEs that occur in fewer than 5% of patients in any treatment group may not be included if a 5% threshold is chosen. The frequency threshold must be less than or equal to the allowed maximum of 5%.
- A participant flow will be created that will describe:
    - Number of participants per treatment arm. Screen failures do not need to be included. Number of participants who did not complete the study per treatment arm. This analysis will be based on study discontinuation, not treatment discontinuation.
    - Reasons participants did not complete the study.

6. References

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.

7. Appendices

Appendix 1. List of Preferred Terms for AESI

AESI	Preferred Term
Cardiac Dysfunction	Acute left ventricular failure
	Acute pulmonary oedema
	Acute right ventricular failure
	Cardiac asthma
	Cardiac failure
	Cardiac failure acute
	Cardiac failure chronic
	Cardiac failure congestive
	Cardiac failure high output
	Cardiogenic shock
	Cardiopulmonary failure
	Cardiorenal syndrome
	Chronic left ventricular failure
	Chronic right ventricular failure
	Cor pulmonale
	Cor pulmonale acute
	Cor pulmonale chronic
	Ejection fraction decreased
	Hepatic congestion
	Hepatojugular reflux
	Left ventricular failure
	Low cardiac output syndrome
	Neonatal cardiac failure
	Obstructive shock
	Pulmonary oedema
	Pulmonary oedema neonatal
	Right ventricular failure
	Ventricular failure
	Artificial heart implant
	Atrial natriuretic peptide abnormal
	Atrial natriuretic peptide increased
	Brain natriuretic peptide abnormal
	Brain natriuretic peptide increased
	Cardiac cirrhosis
	Cardiac index decreased
	Cardiac output decreased
	Cardiac resynchronisation therapy
	Cardiac ventriculogram abnormal
	Cardiac ventriculogram left abnormal
	Cardiac ventriculogram right abnormal
	Cardiomegaly

AESI	Preferred Term
	Cardio-respiratory distress
	Cardiothoracic ratio increased
	Central venous pressure increased
	Diastolic dysfunction
	Dilatation ventricular
	Dyspnoea paroxysmal nocturnal
	Heart transplant
	Hepatic vein dilatation
	Jugular vein distension
	Left ventricular dysfunction
	Myocardial depression
	Nocturnal dyspnoea
	N-terminal prohormone brain natriuretic peptide abnormal
	N-terminal prohormone brain natriuretic peptide increased
	Oedema
	Oedema due to cardiac disease
	Oedema neonatal
	Oedema peripheral
	Orthopnoea
	Peripheral oedema neonatal
	Pulmonary congestion
	Right ventricular dysfunction
	Scan myocardial perfusion abnormal
	Stroke volume decreased
	Systolic dysfunction
	Venous pressure increased
	Venous pressure jugular abnormal
	Venous pressure jugular increased
	Ventricular assist device insertion
	Ventricular dysfunction
	Ventricular dyssynchrony
Cardiac Arrhythmias	Chronotropic incompetence
	Electrocardiogram repolarisation abnormality
	Electrocardiogram RR interval prolonged
	Electrocardiogram U-wave abnormality
	Sudden cardiac death
	Bradycardia
	Cardiac arrest
	Cardiac death
	Cardiac telemetry abnormal
	Cardio-respiratory arrest
	Electrocardiogram abnormal
	Electrocardiogram ambulatory abnormal

AESI	Preferred Term
	Electrocardiogram change
	Heart rate abnormal
	Heart rate decreased
	Heart rate increased
	Loss of consciousness
	Palpitations
	Rebound tachycardia
	Sudden death
	Syncope
	Tachycardia
	Tachycardia paroxysmal
	Bradyarrhythmia
	Ventricular asystole
	Accessory cardiac pathway
	Adams-Stokes syndrome
	Agonal rhythm
	Atrial conduction time prolongation
	Atrioventricular block
	Atrioventricular block complete
	Atrioventricular block first degree
	Atrioventricular block second degree
	Atrioventricular conduction time shortened
	Atrioventricular dissociation
	Bifascicular block
	Brugada syndrome
	Bundle branch block
	Bundle branch block bilateral
	Bundle branch block left
	Bundle branch block right
	Conduction disorder
	Defect conduction intraventricular
	Electrocardiogram delta waves abnormal
	Electrocardiogram PQ interval prolonged
	Electrocardiogram PQ interval shortened
	Electrocardiogram PR prolongation
	Electrocardiogram PR shortened
	Electrocardiogram QRS complex prolonged
	Electrocardiogram QT prolonged
	Electrocardiogram repolarisation abnormality
	Lenegre's disease
	Long QT syndrome
	Sinoatrial block
	Trifascicular block
	Ventricular dyssynchrony
	Wolff-Parkinson-White syndrome

AESI	Preferred Term
	Nodal arrhythmia
	Nodal rhythm
	Sick sinus syndrome
	Sinus arrest
	Sinus arrhythmia
	Sinus bradycardia
	Wandering pacemaker
	Arrhythmia
	Heart alternation
	Heart rate irregular
	Pacemaker generated arrhythmia
	Pacemaker syndrome
	Paroxysmal arrhythmia
	Pulseless electrical activity
	Reperfusion arrhythmia
	Withdrawal arrhythmia
	Arrhythmia supraventricular
	Atrial fibrillation
	Atrial flutter
	Atrial parasystole
	Atrial tachycardia
	Junctional ectopic tachycardia
	Sinus tachycardia
	Supraventricular extrasystoles
	Supraventricular tachyarrhythmia
	Supraventricular tachycardia
	ECG P wave inverted
	Electrocardiogram P wave abnormal
	Retrograde p-waves
	Anomalous atrioventricular excitation
	Cardiac flutter
	Extrasystoles
	Tachyarrhythmia
	Accelerated idioventricular rhythm
	Cardiac fibrillation
	Parasystole
	Rhythm idioventricular
	Torsade de pointes
	Ventricular arrhythmia
	Ventricular extrasystoles
	Ventricular fibrillation
	Ventricular flutter
	Ventricular parasystole
	Ventricular pre-excitation
	Ventricular tachyarrhythmia

AESI	Preferred Term
	Ventricular tachycardia
Encephalopathy	Blurred vision
	Coma
	Confusion
	Extrapyramidal symptoms
	Hallucinations
	Psychotic behavior
	Seizures
	Somnolence
	Urinary incontinence
Infusion-related Reactions	Allergic oedema
	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
	Angioedema
	Ciculatory collapse
	Circumoral oedema
	Conjunctival oedema
	Corneal oedema
	Cytokine release syndrome
	Dialysis membrane reaction
	Distributive shock
	Drug hypersensitivity
	Epiglottic oedema
	Eye oedema
	Eye swelling
	Eyelid oedema
	Face oedema
	Gingival oedema
	Gingival swelling
	Gleich's syndrome
	Hypersensitivity
	Idiopathic urticaria
	Infusion related reaction
	Kounis syndrome
	Laryngeal oedema
	Laryngotracheal oedema
	Limbal swelling
	Lip oedema
	Lip swelling
	Oculorespiratory syndrome
	Oedema mouth
	Oropharyngeal swelling
	Palatal oedema

AESI	Preferred Term
	Periobital oedema
	Pharyngeal oedema
	Scleral oedema
	Shock
	Swelling face
	Swollen tongue
	Tongue oedema
	Tracheal oedema
	Type 1 hypersensitivity
	Urticaria
	Urticaria cholinergic
	Urticaria chronic
	Urticaria popular
Renal toxicity: Nephrotoxicity	Acute renal failure
	Aminoaciduria
	Chronic renal failure Cylindruria
	Decrease in glomerular filtration rate
	Enzymuria
	Fanconi syndrome
	Glycosuria
	Increased serum creatinine
	Phosphaturia
	Proteinuria
	Renal dysfunction
	Tubular acidosis
	Tubulointerstitial nephritis
Renal toxicity: Urotoxicity	Hemorrhagic cystitis
	Hematuria
	RBC in urine

Appendix 2. List of Preferred Terms for Consolidated AE

Consolidated AE	Preferred Term
Abdominal pain	Abdominal pain
	Abdominal pain lower
	Abdominal pain upper
Anaemia	Anaemia
	Haemoglobin decreased
	Red blood cell count decrease
Fatigue	Asthenia
	Fatigue
Hyperbilirubinaemia	Blood bilirubin increased
	Hyperbilirubinaemia
Hypertension	Hypertension
	Blood pressure increased
Hypoalbuminaemia	Blood albumin decreased
	Hypoalbuminaemia
Hypokalaemia	Blood potassium decreased
	Hypokalaemia
Hypomagnesaemia	Blood magnesium decreased
	Hypomagnesaemia
	Magnesium deficiency
Hyponatraemia	Blood sodium decreased
	Hyponatraemia
Hypoproteinemia	Hypoproteinemia
	Protein total decreased
Intestinal obstruction	Gastrointestinal obstruction
	Intestinal obstruction
	Small intestinal obstruction
Leukocytosis	Leukocytosis
	White blood cell count increased
Leukopenia	Leukopenia
	White blood cell count decreased
Lymphopenia	Lymphocyte count decreased
	Lymphopenia
Mucositis	Aphthous stomatitis
	Mucosal inflammation
	Oropharyngeal pain
	Stomatitis
Musculoskeletal pain	Arthralgia
	Back Pain
	Bone Pain
	Flank Pain
	Groin Pain

Consolidated AE	Preferred Term
	Muscle Spasms
	Musculoskeletal Chest Pain
	Musculoskeletal Pain
	Myalgia
	Neck Pain
	Pain In Extremity
Neuropathy	Hypoaesthesia
	Neuropathy peripheral
	Paraesthesia
	Peripheral sensory neuropathy
Neutropenia	Neutropenia
	Neutrophil count decreased
Rash	Dermatitis
	Dermatitis acneiform
	Dermatitis allergic
	Dermatitis bullous
	Rash
	Rash follicular
	Rash generalised
	Rash macular
	Rash papular
	Rash pruritic
	Rash pustular
Thrombocytopenia	Platelet count decreased
	Thrombocytopenia

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