Statistical Analysis Plan

BAT1706-003-CR

A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PHASE III STUDY OF BAT1706 VERSUS EU AVASTIN® PLUS CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Author: Aiqin Zhang, Senior Biostatistician, IQVIA
Todd Dumas, Research Pharmacokineticist, IQIVA

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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	Name	Signature	Date
Author:	Aiqin Zhang		
Position:	Senior Biostatistician		
Company:	IQVIA		
	Name	**Signature**	**Date**
Author:	Todd Dumas		
Position:	Research Pharmacokineticist		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Lawrence Chang		
Position:	Senior Biostatistician		
Company:	IQVIA		
	Name	**Signature**	**Date**
Approved By:	Li Zhang	Li Zhang/张丽	09 Jan 2020
Position:	Chief Medical Officer		
Company:	Bio-Thera Solutions, Ltd.		

OUTPUT SHELLS SIGNATURE PAGE

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	Name	Signature	Date
Author:	Aiqin Zhang		
Position:	Senior Biostatistician		
Company:	IQVIA		

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Approved By:	Lawrence Chang		
Position:	Senior Biostatistician		
Company:	IQVIA		
	Name	**Signature**	**Date**
Approved By:	Li Zhang	Li Zhang	09 Jan 2020
Position:	Chief Medical Officer		
Company:	Bio-Thera Solutions, Ltd.		
	Name	**Signature**	**Date**
Approved By:	Qingsong He		09 Jan 2020
Position	Project Manager		
Company	Bio-Thera Solutions, Ltd.		

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Contents

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
CFDA	China food and drug administration
CI	Confidence interval
CIR	Central imaging review
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CRF	Electronic case report form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EoT	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
GCP	Good Clinical Practice

HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LTE	Long-Term Extension
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NADA	Neutralizing anti-drug antibody
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
nsNSCLC	Non-squamous non-small cell lung cancer
ORR	Overall response rate
ORR_6	Overall response rate at Week 6
ORR_{12}	Overall response rate at Week 12
ORR_{18}	Overall response rate at Week 18
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
popPK	population pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome

PT	Prothrombin time
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOP	Standard operating procedures
TEAEs	Treatment-emergent adverse events
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

2. INTRODUCTION

The purpose of this SAP is to document technical and detailed specifications for the final analysis of data collected for protocol BAT1706 003-CR, Version 5.0, 20Jun2019.

Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

The SAP is based upon section 9 (Statistics) of the trial protocol and prepared in compliance with ICH E9.

2.1. PRIMARY OBJECTIVE

The primary objectives are to:

- Compare the efficacy of BAT1706 and EU-Avastin® given with chemotherapy as first line treatment using the ratio or the difference in ORR to show clinical equivalence.

2.2. SECONDARY OBJECTIVES

The secondary objectives are to:

- Evaluate the efficacy of BAT1706 and EU-Avastin® given with chemotherapy using ORR at different time points, duration of response (DoR), PFS, and OS (time, and rate at 12 months).
- Evaluate the safety and immunogenicity of BAT1706 and EU-Avastin®.
- Characterize bevacizumab exposure after administration of BAT1706 and EU-Avastin®.

2.3. EXPLORATORY OBJECTIVES

- To explore population pharmacokinetics (popPK).

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, randomized, double-blind, multi-center, active comparator, parallel two-arm study to compare the efficacy, and to evaluate the safety and immunogenicity of BAT1706 to EU-Avastin® in patients with previously untreated advanced non-squamous non-small cell lung cancer (nsNSCLC) to demonstrate clinical equivalence of BAT1706 and EU-Avastin®.

3.2. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

After stratification for disease stage (IV vs. other), gender (male vs. female) and ethnicity (Asian vs non-Asian), eligible patients will be randomized in a 1:1 ratio to receive BAT1706 plus paclitaxel and carboplatin (Arm A) or EU-Avastin® plus paclitaxel and carboplatin (Arm B). Patients will be assessed for histology and randomization will occur after central imaging review (CIR) to confirm the presence of at least one measurable target lesion

according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

3.3. TREATMENTS ADMINISTERED

Combination treatment will be administered every 3 weeks up to 6 cycles, followed for those with non-progressive disease with maintenance monotherapy with BAT1706 or EU-Avastin® until a maximum of total study treatment of 12 months (17 cycles). Patients intolerant to chemotherapy after 2 dose reductions can start monotherapy with BAT1706 or EU-Avastin® or start another line of anti-cancer therapy after investigator's judgment.

A data safety monitoring board (DSMB) will review all safety data after the first 20 patients have been treated for 6 weeks in each arm; then after, if no unexpected safety signal was identified, the study will continue, and the safety data will be reviewed at regular intervals after approximately every 200 patients are evaluated after they received the first 4 cycles.

3.4. SCHEDULE OF EVENTS

Patients will undergo tumor assessment at Weeks 6, 12 and 18, regardless of the number of cycles actually completed (with a visit window of 1 week maximum during the first 18 weeks), then after every 3 cycles (approximately every 9 weeks) and at SFUV/EoT. During the trial, tumor response will be assessed by local radiologist/Investigator for immediate therapeutic decision.

To comply with the different statistical approaches of each regulatory agency, the main efficacy analyses (difference and ratio of ORR) will be based upon tumor response at different time points as determined by CIR according to RECIST 1.1. After Week 18, patients with responding or stabilized disease will remain in the study until a total study treatment duration of 12 months is reached to provide further comparative safety/immunogenicity data as well as other efficacy parameters (such as DoR, PFS and OS rates at 12 months for both BAT1706 and EU Avastin®).

All patients will remain in the study until Investigator assessed disease progression, excessive toxicity, Investigator's judgment, withdrawal of consent, lost to follow-up, death, start of a new anticancer therapy, study termination by the Sponsor, or for a maximum of 12 months of treatment, whichever occurs first. Then after, all patients who are still benefiting of therapy will have the option to continue treatment with BAT1706 in a LTE study (as of Week 53) until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for a maximum of 12 additional months (ie, for up to 24 months from initial randomization).

Survival Follow up will occur every 3 months until 24 months after randomization. A complete clinical study report will be submitted to the China Food and Drug Administration (CFDA), United States (US) Food and Drug Administration (FDA), and the European Medicines Agency (EMA) when primary efficacy data are available in all patients. At the end of the LTE, a complementary study report will be released. The study will be conducted according to the national and international ethical standards, the Good Clinical Practice guidelines, and the protocol will be approved by the Institutional Review Boards/Independent Ethics Committees of the participating sites.

The schedule of events can be found in Table 1 and Table 2 in the protocol BAT1706 003-CR, Version 5.0, 20Jun2019.

3.5. CHANGES TO ANALYSIS FROM PROTOCOL

NOT APPLICABLE.

4. PLANNED ANALYSES

The following formal analyses are planned for the study:

4.1. DSMB ANALYSIS AND DATA MONITORING

[redacted]

4.2. PRIMARY EFFICACY ENDPOINT AND SECONDARY ENDPOINTS FINAL ANALYSIS

A final analysis of efficacy, safety, pharmacokinetics, immunogenicity and survival data will be performed by IQVIA Biostatistics following Sponsor authorization based on all data (up to a maximum of one year of treatment) available after the last patient enrolled has completed the Week 18 evaluation, provided there are safety and immunogenicity data for one year from enrollment for at least one-third of the study population. Data through the above said data cut off point will be locked, the unblinded team will produce the results, and the results will be shared with the Sponsor. Following Sponsor authorization, a complete clinical study report will be released.

4.3. FOLLOW-UP ANALYSIS

A follow-up analysis including all secondary efficacy (survival and duration of response), safety, pharmacokinetics and immunogenicity will be performed by IQVIA Biostatistics after the last patient has completed the Long-Term Extension (LTE) study or at the latest 24 months after randomization of the last patient. Following Sponsor authorization, a complementary clinical study report will be released and archived. The data collected in the LTE study will be presented using separate TFLs based on corresponding TFLs of secondary endpoints analysis.

5. ANALYSIS SETS AND SUBGROUPS

The following subject sets are applicable to this study:

5.1. SCREENED ANALYSIS SET (SCR)

The Screened Analysis Set will consist of all subjects who signed the informed consent.

5.2. INTENTION-TO-TREAT POPULATION (ITT)

The ITT Population will consist of all randomized patients in accordance with the intended treatment arm, regardless of the treatment actually received. For the primary efficacy analysis of the ITT population, patients who discontinued prior to Week 18 for any reason will be counted as non-responders.

5.3. PER-PROTOCOL POPULATION (PP)

The PP population is defined as patients who have received at least 3 cycles of study drugs as allocated (BAT1706 or EU Avastin® and paclitaxel/carboplatin) or less due to early progression, death, or excessive toxicity and have one tumor assessment with no major protocol deviations that would have significantly impact on primary efficacy or safety outcomes.

All decisions to exclude patients from PP population will be made prior to database release. For the PP efficacy analysis, patients for whom the efficacy endpoint is missing, i.e., patients without at least 1 valid post treatment evaluation, are excluded from the PP population, except those who are withdrawn due to excessive toxicity, early progression or death, in which case the patients will be classified as non-responders. It is anticipated that approximately 10% of patients in the ITT population will be excluded from the PP Population.

If the Per Protocol analysis set includes at least 90% of subjects in the ITT Population, additional efficacy analyses on the Per Protocol analysis set will be omitted as the differences in the results based upon these

two analysis sets are expected to be negligible.

5.4. SAFETY POPULATION (SAF)

The Safety Population will consist of all randomized patients who received at least one dose of study drug (BAT1706 or EU-Avastin®) and allocated into actual-received treatment arm. The safety population will be used as the basis for all safety analyses.

5.5. PHARMACOKINETIC (PK) POPULATION

Pharmacokinetic population is a subgroup of 200 patients from samples collected only at designated sites in China, Turkey, and Ukraine who receive at least one dose of study drug, have at least one measured concentration at a scheduled post dose PK time point, and have no major protocol deviations that may significantly affect the PK assessment. The PK and optional popPK analysis will be performed on the PK population.

5.6. POPULATION PHARMACOKINETIC (POPPK) POPULATION

Optional exploratory popPK analyses may be conducted to support drug approval for other countries. Details and criteria for popPK population would be outlined in a separate standalone modelling analysis plan with the results reported separately from the Clinical Study Report if conducted.

6. GENERAL CONSIDERATIONS

6.1. TREATMENT ARMS

- Treatment Arm A: BAT1706 plus carboplatin and paclitaxel.
- Treatment Arm B: EU-Avastin® plus carboplatin and paclitaxel.

6.2. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the day of the first administration of study treatment, (Day 1 is the day of the first dose of study treatment) and will appear in every listing where an assessment date or event date appears.

Study day will be calculated from the reference start date and will be used to show start/stop day of the assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference date, then:
  Study day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference treatment start date (including unscheduled assessments). In case where the last non-missing measurement and the reference treatment start date coincide, that measurement will be considered as baseline, but AEs and medications commencing on the reference start date will be considered post-baseline, that is, treatment-emergent or concomitant ("worst case" approach).

For ECG results, if last non-missing measurement and the reference treatment start date coincide, that measurement must be pre-treatment in order to be considered as baseline.

6.4. END OF TREATMENT

All patients who receive at least one infusion of BAT1706 or EU-Avastin® and who discontinue the study at any time after Day 1 (but do not withdraw their consent) will be required to undergo all of the evaluations for the SFUV/EoT that will take place 28 days ± 2 days after they received the last dose during the study with a maximum at Week 53.

6.5. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit (cycle X day X) summaries but will contribute to best/worst case value where required (e.g., shift table).

In the case of a retest (visit-specific unscheduled visit number assigned), the latest non-missing measurement among all scheduled and unscheduled measurements for that visit will be used for by-visit summaries.

For any subject with early withdrawal assessments available, all early withdrawal assessments related to the specific subject are to be considered in chronological order and are to be:

- Considered as unscheduled.
- Not summarized in the by-visit summaries.
- Only listed in the by-subject data listings.

Listings will include scheduled, unscheduled, retest, and early discontinuation data.

6.6. STATISTICAL TESTS

The significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from Baseline will be calculated as:

- Change from baseline = Test Value at Visit X – Baseline Value

For quantitative measurements, % change from baseline will be calculated as:

- (Test value at visit X – test value on baseline)/test value on baseline * 100%

The time from Date of Event A to Date of Event B (years) is calculated as:

- (Date of Event B - Date of Event A + 1)/365.25.

The time from Date of Event A to Date of Event B (months) is calculated as:

- (Date of Event B - Date of Event A + 1)/30.4375.

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS Version 9.4, except for the PK analysis. Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 6.4 or higher (Certara, Princeton, New Jersey, United States). Figures may be prepared using SAS®, Phoenix® WinNonlin®, or SigmaPlot 12.5 or higher (Systat Software, Inc., San Jose, California, United States).

7. STATISTICAL CONSIDERATIONS

7.1. HYPOTHESIS

The null hypothesis is that either (1) BAT1706 is inferior to EU-Avastin® or (2) BAT1706 is superior to EU-Avastin® based on a pre-specified equivalence margin.

To satisfy the different methods used by the regulatory agencies, different endpoints and methods of calculations will be used in this global study.

To satisfy the CFDA and US FDA statistical approaches, the null hypothesis will be rejected if the 90% confidence interval (CI) for the ratio of ORR_{18} (BAT1706: EU-Avastin®) fall completely within the predefined equivalence margin of (0.75, 1.33) to comply with CFDA requirements and within the predefined equivalence margin of (0.73, 1.36) to comply with FDA requirements. To satisfy the European Medicines Agency (EMA) statistical approach, the null hypothesis will be rejected if the 95% CI of the difference in the ORR_{18} between treatments (BAT1706 and EU-Avastin®) is entirely contained within the predefined equivalence margin of (-0.12, 0.15).

The alternative hypothesis is that BAT1706 is equivalent to EU-Avastin®, which can be demonstrated by showing that the true treatment ratio/difference is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference.

7.2. SAMPLE SIZE

Approximately 632 patients will be enrolled including [redacted]

7.2.1. DETERMINATION OF SAMPLE SIZE

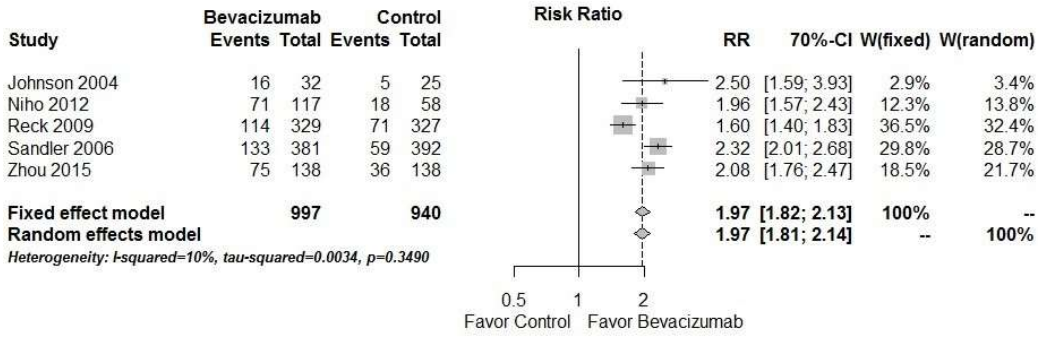
The expected ORR used for this study is based on the ORR calculated from our meta-analysis that includes a population of Western and Asian patients (with approximately 23% of Asian patients) with nsNSCLC cancer and unknown EGFR/ALK mutation status. Such an ORR is derived from the reported best ORR in the intent-to-treat (ITT) population or in the subgroup of patients with measurable disease. Although enrolling a higher rate of Asian patients, which would yield an ORR of about 45%, we expect the ORR in our study to be approximately 40% since we will exclude patients with known EGFR mutation or ALK receptor alteration (conferring slightly higher, non-statistically significant, responsiveness) in regions where the targeted agents are available.

To satisfy all regulatory agencies (CFDA, EMA, and US FDA), results will be presented using the risk ratio or the

risk difference method to show equivalence.

7.2.2. SAMPLE SIZE JUSTIFICATION BASED ON RISK RATIO

To satisfy the CFDA and US FDA, equivalence will be demonstrated using the risk ratio method. The net treatment effect of Avastin® as measured by the ratio of ORRs is 1.97 with a corresponding 70% CI of (1.81, 2.14). Preserving 52% net effect of Avastin®, the equivalence margin will be set to 1.33 on the ratio of ORRs. Preserving 48% net effect of Avastin®, the equivalence margin will be set to 1.36 on the ratio of ORRs.

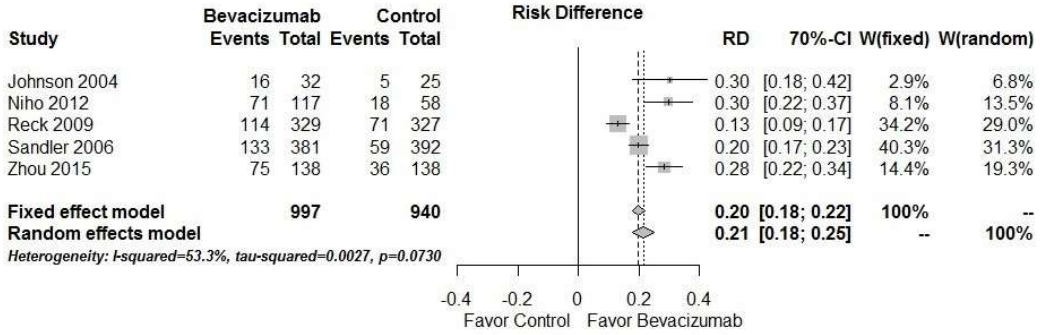


Abbreviations: CI = confidence interval; RR = risk ratio.

The null hypothesis is that either (1) BAT1706 is inferior to Avastin® or (2) BAT1706 is superior to Avastin® based on a pre-specified equivalence margin of (0.75, 1.33) for CFDA, and based on a pre-specified equivalence margin of (0.73, 1.36) for US FDA. The alternative hypothesis is that BAT1706 is equivalent to Avastin®, which can be demonstrated by showing that the true treatment ratio is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence will be declared if the 2-sided 90% CI of the ratio of ORRs (BAT1706: Avastin®) is entirely contained within the equivalence margin of (0.75, 1.33) for CFDA, and within the equivalence margin of (0.73, 1.36) for US FDA. Based on these equivalence margins and reference effect size of 40%, 316 patients per arm (632 patients total) will achieve 80% power for CFDA and will achieve 87% power for US FDA. The primary analysis will be based on the ITT population, and the supportive analysis will be based on the per-protocol (PP) population. With an expected ORR of 42% in the PP set, 83% power will be achieved with the equivalence margin of (0.75, 1.33), and 90% power will be achieved with the equivalence margin of (0.73, 1.36).

7.2.3. SAMPLE SIZE JUSTIFICATION BASED ON RISK DIFFERENCE

To satisfy the EMA, equivalence will be demonstrated using the risk difference method. The net treatment effect of Avastin® as measured by the difference between ORRs is 0.21 with 70% CI of (0.17, 0.26). Preserving 29% net effect of Avastin®, the equivalence margin will be set to (-0.12, +0.15) for the difference of ORRs.



Abbreviations: CI = confidence interval; RD = risk difference.

The null hypothesis is that either (1) BAT1706 is inferior to EU Avastin® or (2) BAT1706 is superior to EU Avastin® based on a pre-specified asymmetrical equivalence margin of (-0.12, 0.15). The alternative hypothesis is that BAT1706 is equivalent to EU Avastin®, which can be demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinical acceptable difference. In other words, equivalence will be declared if the 2-sided 95% CI of the difference in the ORR between treatments (BAT1706 and EU Avastin®) is entirely contained within the equivalence margin of (-0.12, 0.15).

Based on that margin and a reference effect size of 40% at Week 18, 316 patients per arm (632 patients total) will achieve 85% power and 2-side control type I error within 5%. The primary analysis will be based on the ITT population, and the supportive analysis will be based on the PP population. With an expected ORR of 42% in the PP set, 84% power will be achieved.

7.3. MULTI-CENTER STUDIES

This is a multi-center study and centers may be pooled together in a country/region level for subgroup or center effect analysis in an exploratory manner if applicable.

7.4. MISSING DATA

Missing safety data will not be imputed.

Missing efficacy data will be handled as described in section 16.4 of this analysis plan.

7.5. EXAMINATION OF SUBGROUPS

The following subgroups are considered of interest to comparatively explore the treatment effect for the definition of subgroups, data as documented in the CRF will be taken.

- Age: <65 years vs. ≥ 65 years
- Baseline ECOG performance status: 0 vs. 1
- nsNSCLC Stage: IV vs. Recurrent disease
- Sex: Male vs. Female
- Ethnicity: Asian vs. Non-Asian
- Planned dose of Paclitaxel (200 vs. 175 mg/m^2)
- Planned dose of Carboplatin (AUC 6 vs. 5 mg/mL·minute)

- Reduced Percentage of paclitaxel dose at cycle 6 from initial dose (>80% vs. ≤80%)
- Reduced Percentage of carboplatin dose at cycle 6 from initial dose (AUC >80% vs. ≤80%)

8. OUTPUT PRESENTATIONS

Appendix 1 details the conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Continuous variables will be summarized using descriptive statistics, i.e.

- Number of subjects (N), number of subjects with non-missing values
- Mean, standard deviation (SD)
- Median,
- 25th Percentile - 75th Percentile (Q1-Q3)
- Minimum and maximum.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

9. DISPOSITION AND WITHDRAWALS & PROTOCOL DEVIATION

9.1. DISPOSITION AND WITHDRAWALS

Patient disposition will be summarized for patients in ITT population. The total number of patients for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the ITT population. Study drug and study duration will be summarized using descriptive statistics for the safety population.

9.2. PROTOCOL DEVIATION

Protocol deviation will be summarized for patients in ITT population. Protocol deviations will be presented in a listing including date, severity and action of population exclusion if any. The protocol deviation which impacts subject safety, ICH-GCP compliance and study endpoints will be marked as important protocol deviation per suggestion's approval prior to database lock. The type of protocol deviations includes the following categories based on IQVIA' SOP:

- Informed consent
- Eligibility and entry criteria
- Concomitant medication criteria
- Laboratory assessment criteria
- Study procedures criteria
- Serious adverse event criteria

- Randomization Criteria
- Visit schedule criteria
- IP compliance
- Efficacy criteria
- Administrative criteria
- Source document criteria
- Regulatory or ethics approvals criteria
- Other criteria

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized for the ITT. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DEMOGRAPHICS

The following demographic data is derived from CRF page "Demographics".

- Age (years) = (Date of ICF signed – Date of Birth +1)/365.25
    - < 65 years
    - >= 65 years
        - 65 - < 75 years
        - 75 - < 85 years
        - >= 85 years
- Sex:
    - Male
    - Female
- Ethnicity:
    - Hispanic or Latino
    - Not Hispanic or Latino
    - Unknown
- Race:
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White
    - Other

10.2. OTHER BASELINE CHARACTERISTICS

- ECOG Performance Status
    - 0

  - 1
  - >1
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) = Weight (kg)/ Height (m)^2

The following infection screen will be summarized for the ITT for overall subjects ("Infection Screen" on eCRF).

- Hepatitis B: positive, negative, unknown.
- Hepatitis C: positive, negative, unknown.
- Human Immunodeficiency Virus (HIV): positive, negative, unknown.
- Syphilis: positive, negative, unknown.
- Tuberculosis: positive, negative, unknown.

10.3. MUTATION STATUS AT BASELINE

The following mutation screen will be summarized for the ITT for overall subjects ("EGFR, ALK and ROS-1 Mutation Status" on eCRF).

- EGFR Mutation: positive, negative, unknown.
- ALK Mutation: positive, negative, unknown.
- ROS-1 Mutation: positive, negative, unknown.

10.4. DERIVATIONS

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days
- Duration (Years) = (Date of Informed Consent Signed – Date of Event + 1)/365.25

11. SURGICAL AND MEDICAL HISTORY

11.1. LUNG CANCER HISTORY

- Time since Initial nsNSCLC diagnosis (months) – calculated relative to date of ICF
- Stage of the disease at the time of initial diagnosis
  - Stage I
  - Stage II
  - Stage III
  - Stage IV
- nsNSCLC Pathology Classification

- Adenocarcinoma
- Large cell carcinoma
- Adenosquamous NSCLC mixed predominant Adenocarcinoma
- Other

- nsNSCLC Stage at Enrolment

Lung cancer history are record on the "Lung Cancer History" CRF page.

11.2. SURGICAL HISTORY

Surgical History are recorded on the "Medical / Surgical History" CRF page.

Medical history still ongoing will be summarized by system organ class (SOC) and preferred term (PT) for the SAF. Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary (MedDRA latest version) will be used for coding. Records will be sorted alphabetically.

Medical history still ongoing at enrolment or ended prior to enrolment will be listed together for the ITT.

12. CONCOMITANT ILLNESSES

Concomitant Illnesses are conditions (other than the indication being studied) which started prior to or at screening and are ongoing at the date of screening, which will be summarized by system organ class (SOC) and preferred term (PT) for the SAF Population. Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary (MedDRA latest version) will be used for coding. Records will be sorted alphabetically. Concomitant Illnesses will be coded using "Medical / Surgical History".

Medical history still ongoing at enrolment or ended prior to enrolment will be listed together for the ITT.

13. MEDICATIONS AND PROCEDURES

13.1. PRIOR ONCOLOGY THERAPIES AND SURGERIES

Prior oncology therapies including chemotherapy, medications, radiotherapy, and procedures will be captured on "Prior Radiotherapy", "Prior Anticancer Therapy" and "Prior Cancer-related Surgeries/Procedures" CRF pages respectively. Only therapies and procedures starting prior to screening visit will be collected. Otherwise the therapy will be presented together with concomitant medications whilst procedures will be considered concomitant procedures.

In addition to coded terms, number of prior oncology chemotherapy and medication per subject will be summarized together with best response for each subject.

Radiotherapies (including best response), surgeries and procedures will be presented and listed for the ITT. In addition, tumor history of surgery and procedures will be coded according to MedDRA (latest version), and summarized by SOC/PT for the ITT.

Prior oncology therapies will be listed for SAF.

13.2. PRIOR MEDICATIONS AND PROCEDURES

WHO drug dictionary (latest version) will be used to classify prior medications by preferred term.

Prior medication is defined as any medication taken prior to the date of first dose of investigational product, will be summarized separately by the number and percentage of subjects receiving each medication within each preferred term by treatment group and overall for the Safety population.

Prior medication usage will be summarized separately by the number and percentage of subjects receiving each medication within each preferred term by treatment group and overall for the ITT. Multiple medication usage by a subject in the same category will be counted only once for the purpose of the summaries.

All prior medications and procedures will be listed for the ITT.

13.3. CONCOMITANT MEDICATIONS AND PROCEDURES

Concomitant medication is defined as all medications taken by the subject from signed informed consent through 28 days after last study treatment.

Concomitant medication (CRF page "Concomitant Medications") usage will be summarized separately by the number and percentage of subjects receiving each medication within each preferred term by treatment group and overall for the Safety population. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once for the purpose of the summaries.

Concomitant Procedures are captured on CRF page "Concomitant Procedures". Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, latest version will be used for coding.

Relevant information for procedures will be listed for the ITT.

14. STUDY MEDICATION EXPOSURE

14.1. TREATMENT EXPOSURE

- BAT1706 will be supplied as 100 mg/4 mL. The dose is 15 mg/kg every 3 weeks.
- EU-Avastin® will be supplied as 100 mg/4 mL. The dose is 15 mg/kg every 3 weeks.
- The initial dose of paclitaxel is 200 mg/m². For Chinese patients (according to local label), paclitaxel will be administered at a dose of 175 mg/m².
- In all patients, the initial dose target of carboplatin is area under the curve (AUC) 6 mg/mL·minute.
- For all patients in case of anticipated excessive toxicity (e.g., elderly patients, prior toxicity during chemo-radiotherapy), the Investigator may start the first course of chemotherapy using paclitaxel at a dose of 175 mg/m² (or use a paclitaxel dose of 200 mg/m² after prophylactic administration of G-CSF), and/or carboplatin AUC 5 mg/mL·minute.

14.2. DERIVATIONS OF TREATMENT EXPOSURE

The summary of treatment exposure and compliance for study drugs will include the following information in the SAF for overall.

- **Treatment duration (week):**

$$\text{Duration of Drug} = \left(\frac{\text{date of last dose of Drug - date of first dose of Drug + 21}}{7}\right)$$

- **Total number of infusions received (n)**

- **Cumulative actual treatment dose (mg/kg):** the sum of the calculated actual dose levels of each drug that the subject received (i.e. total dose administered (mg/kg))

- **Dose intensity (DI) (mg/kg/week)** per subject is defined as:

$$DI = \left(\frac{\text{Cumulative dose of Drug from 1st infusion}}{\text{(date of last dose of Drug – date of first dose of Drug + 21) / 7}}\right)$$

- **Relative dose intensity (RDI) (%)** per subject is defined as the actual dose intensity divided by the planned dose per week and expressed in %.

$$RDI = 100 \text{ X } \left(\frac{\text{Dose Intensity}}{15/3}\right)$$

15. STUDY MEDICATION COMPLIANCE

Compliance to study medication will be presented for the Safety Population.

Compliance to study medication will adopt the relative dose intensity (RDI) in section 14.2.

16. EFFICACY OUTCOMES

The efficacy analyses will be applied for both the PP and ITT Population.

Treatment efficacy will be evaluated using tumor responses. Tumor response will be assessed by the local Investigator and/or radiologist according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; see protocol Appendix 13.4) for immediate therapeutic decision. However, the primary efficacy analysis will be based upon the evaluation of tumor response as determined by CIR. Patients will undergo tumor assessment at Weeks 6, 12 and 18, regardless of the number of cycles actually completed, then after every 3 cycles (approximately every 9 weeks) and at Safety Follow-up Visit (SFUV)/End of Treatment (EoT). Window for tumor assessment is 1 week at the maximum during the first 18 weeks.

Tumor responses data are captured on CRF page “Tumor Evaluation Target Lesions”, “Tumor Evaluation Non-Target Lesions”, “Tumor Evaluation New Lesions”, and “Overall Tumor Response (According to RECIST 1.1)”. Tumor assessment results from each scheduled visit will be listed for SAF. Tumor assessment for target lesion including sum of diameters for each cycle will be summarized for the SAF.

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy endpoint is ORR at Week 18 (ORR_{18}) based on tumor response evaluated according to RECIST 1.1 (Appendix 13.4 in protocol) as assessed by CIR.

To demonstrate equivalence between BAT1706 and EU-Avastin® arms, the ratio of, as well as the difference between ORR_{18} will be analyzed. Equivalence will be declared if the 90% confidence interval (CI) of the ratio of ORR_{18} (BAT1706:EU-Avastin®) is entirely contained within the equivalence margin of (0.75, 1.33) to comply with CFDA requirements, and within the equivalence margin of (0.73, 1.36) to comply with US FDA requirements. The

difference in ORR_{18} will be calculated, and equivalence will be declared if the 95% CI of the difference in the ORR_{18} between treatments is entirely contained within the asymmetrical equivalence margin of (-0.12, 0.15) to comply with EMA requirements.

Response Week 18 will be based on tumor assessment obtained at Week 18. Patients not achieving Week 18 assessment will be considered non-responders if they dropped out earlier in case of intolerance, documented disease progression, withdrawal of consent, lost to follow up, or death.

The ORR_{18} is calculated as the proportion of patients achieving a PR or a CR at Week 18. Confirmation of response is not required.

16.1.2. PRIMARY EFFICACY ANALYSES

The primary efficacy analyses aim to demonstrate the equivalence between BAT1706 and EU Avastin® arms. The null hypothesis tested for the primary efficacy analyses is that either (1) BAT1706 is inferior to EU Avastin® or (2) BAT1706 is superior to EU Avastin® based on a predefined equivalence margin.

For the CFDA and US FDA, to demonstrate equivalence between the 2 treatment groups, the ratio of ORR will be used. The ratio of ORR18 will be calculated.

The 2-sided 90% CI of risk ratio or 95% CI of risk difference will be estimated including covariates of stratification factors: NSCLC stage (recurrent disease after any stage at time of primary diagnosis, or stage IV), gender (male or female), and ethnicity (Asian or non-Asian) for the ITT population as primary analyses and for the PP population as supportive analyses.

The multivariate-adjusted risk ratio and the 90% CI will be estimated by the log-binomial regression model including stratification factors. When the log-binomial model fails to converge, the Poisson regression with robust error variance will be used.

The multivariate-adjusted risk difference and the 95% CI will be estimated by the binomial regression model including stratification factors. If this binomial model for the risk difference fails to converge, the modified Poisson approach can be used as above.

The primary efficacy analyses will take place after all patients have been evaluated for response at Week 18.

The sample code can be found in appendix 5: Sample Code for Efficacy Analysis.

16.2. SECONDARY EFFICACY

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The secondary efficacy endpoints include ORR_6 , ORR_{12} , best ORR of confirmed responses at end of study, DoR, PFS rate at 12 months, PFS time, OS rate at 12 months, and OS time.

Response at Week 6 will also be evaluated by CIR to provide ORR_6 to show the pattern of response. After Week 18, patients with responding or stabilized disease will remain in the study up to 12 months to provide further comparative safety/immunogenicity data as well as other efficacy parameters (such as DoR, PFS and OS rates at 12 months for both BAT1706 and EU-Avastin®).

A SFUV/EoT visit will take place 28 days ± 2 days after the last dose during the study with a maximum at Week 53. Patients who are still benefiting of therapy after 12 months of treatment will have the option to continue treatment with BAT1706 as of Week 53 after SFUV (regardless of the arm they were assigned to at randomization) in a Long term extension (LTE) study until disease progression, excessive toxicity, withdrawal of consent, Investigator's decision, or for an additional 12-month period (ie, for a maximum of 24 months from initial randomization).

The secondary binomial efficacy endpoints will be summarized descriptively and analyzed similarly to the primary efficacy endpoint. For time to event variables such as PFS, OS, and DoR, Kaplan Meier curves will be calculated and displayed. Median survival times and the corresponding 95% CI will be provided. The estimated hazard ratio with 95% CI will be obtained from Cox regression model. The secondary analyses will be conducted based on data from up to 12-month exposure. For both analyses, data from all 632 randomized patients will be analyzed. A complementary report for safety and survival data will be made 2 years after LPI.

The secondary efficacy endpoints are as follows:

- Progression free survival rate at 12 months, defined as the proportion of patients being alive without documented progression 12 months after randomization, using Kaplan-Meier method.
- Progression free survival time defined as the time from the date of randomization to the date of documented clinical or radiological progression or death due to any cause using Kaplan-Meier method.
- Overall survival rate at 12 months, defined as the proportion of patients being alive 12 months after randomization using Kaplan-Meier method.
- Overall survival time defined as the time from randomization to death of any cause using Kaplan-Meier method.
- ORR at Week 6 (ORR_6) and ORR at Week 12 (ORR_{12}), based on tumor response as assessed by CIR, and best ORR of confirmed responses at end of study assessed by local radiologist/Investigator if after Week 18 according to RECIST 1.1.
- Duration of response defined as the time from first documentation of a response (CR or PR) and the first documentation of progression (assessed by local radiologist/Investigator if after Week 18) according to RECIST 1.1.

16.2.2. SECONDARY EFFICACY ANALYSES

23.1.1.1. Overall Response Rate (ORR)

Overall response rate will be the proportion of subject with a best overall response of CR or PR. The ORR and its 95% confidence interval (CI) will be presented. The 95% (exact) CI will be calculated based on the binomial method. When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time-point. ORR_6 and ORR_{12} will be analysed base on CIR assessment.

23.1.1.2. Progression Free Survival (PFS)

Progression-free survival is defined as the time from the date of randomization to disease progression or death whichever occurs first in subjects. Subjects without event (no disease progression or death) will be censored at the date of 'last tumor assessment'. Subjects for whom no post-baseline tumor assessments are available are censored at the time of first dose. Kaplan Meier methodology will be used to estimate median PFS and its 95% confidence interval. Kaplan Meier curves will be constructed to provide a visual description of the PFS change with time. PFS will be analysed based on Investigator assessment.

- **Define date of PFS event / censoring:**

Status		Censoring	Date of event / censoring
Progressed or died	Within two subsequent scheduled tumor assessments after last response assessment of CR, PR or SD or randomization	Event	Minimum(Date of PD, Date of death)

	Otherwise	Censored	Date of last tumor assessment with outcome CR, PR or SD or date of randomization, whatever is later
Neither progressed nor died		Censored	Date of last tumor assessment with outcome CR, PR or SD or date of randomization, whatever is later

23.1.1.3. Overall Survival (OS)

Overall survival is defined as the time from randomization to the date of death (any cause). Subjects who were alive at the time of analysis or end of study will be censored at the date of the last available visit. Kaplan-Meier methodology will be used to estimate the median survival time and its 95% confidence interval. Kaplan Meier curves will be constructed to provide a visual description of the OS change with time. OS will be analysed based on Investigator assessment.

- **Define date of OS event / censoring:**

Survival Status		Censoring	Date of event/censoring
Died	Before cut-off	Event	Date of death
	After cutoff	Censored	Date of cutoff
Alive (no date of death)	Alive after cut-off	Censored	Date of cut-off
	Otherwise	Censored	Last date known to be alive

23.1.1.4. Duration of Response (DoR)

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of disease progression of death for any cause, whichever occurs earlier. For subjects who are alive without disease progression following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment or last follow-up for progression of disease. Kaplan Meier methodology will be used to estimate median duration of response or duration of stable disease and its 95% confidence interval. Kaplan Meier curves will be constructed to provide a visual description of the DoR.

DOR will be analysed based on CIR assessment before week 18 and investigator assessment after week 18.

23.1.1.5. Best Overall Response (BOR)

The BOR for each subject is defined as the best result obtained among all tumor assessments from the randomization until documented disease progression. The overall response will be based on imaging, classified according to RECIST version 1.1 criteria.

The best possible overall response is CR, followed by PR, SD and PD. If a subject has missing baseline tumor assessment and/or no tumor assessment on-treatment, BOR will be Not Evaluable (NE). In the case the single response is SD, SD must have been assessed no less than 6 weeks (at least 42 days) after randomization, otherwise the best response will be NE. In case of different dates of scans within the same tumor assessment, the latest date will be used for diagnosis of response and the earliest date for date of progression.

The BOR rate is defined as the number of subjects, whom BOR was either Complete Response (CR) or Partial Response (PR), confirmed at end of treatment (EoT) assessed by local radiologist/Investigator if after Week 18 according to RECIST 1.1. BOR will be analysed based on CIR assessment before week 18 and investigator assessment after week 18.

16.3. SUBGROUP ANALYSES

The primary endpoint and secondary endpoints will be also analyzed in subgroups breaking down by, but not limited to, country/region/demographic, dose of paclitaxel and carboplatin, or stratification factors: Stage (IV or other), gender and ethnicity (Asian or non-Asian).

In each subgroup, the analysis will be carried out using the same type of methodology as described for corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of patients, the analysis may not be performed.

One additional exploratory analysis to assess the effect of paclitaxel dose differences and carboplatin dose differences on the primary endpoint will be conducted by fitting a logistic regression model of ORR_{18} with independent factors including paclitaxel dose (200 vs 175 mg/m^2), carboplatin dose (AUC 6 vs 5 mg/mL·minute), treatment group, and ethnicity (Asian vs non-Asian). Odds ratios and 95% confidence intervals will be presented.

Another exploratory analysis to assess the effect of reduced dose of paclitaxel and carboplatin on the primary endpoint will be conducted by a logistic regression model of ORR_{18} with independent factors including paclitaxel dose (>80% vs ≤80% of initial dose at cycle 6), carboplatin dose (AUC >80% vs ≤80% of initial dose at cycle 6), treatment group, and ethnicity (Asian vs non-Asian).

The primary endpoint and secondary endpoints will be also analyzed in subgroups breaking down by stratification factors:

- Age (<65 vs. ≥65 years),
- ECOG Performance Status (0 vs. 1),
- nsNSCLC Stage (IV vs. Recurrent disease)
- Sex (male vs. female)
- Ethnicity (Asian vs. non-Asian).
- Planned dose of Paclitaxel (200 vs. 175 mg/m^2)
- Planned dose of Carboplatin (AUC 6 vs. 5 mg/mL·minute)
- Reduced Percentage of paclitaxel dose at cycle 6 from initial dose (>80% vs. ≤80%)
- Reduced Percentage of carboplatin dose at cycle 6 from initial dose (AUC >80% vs. ≤80%)

These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of patients, the analysis may not be performed.

16.4. MISSING DATA METHODS OF EFFICACY

For the primary efficacy analysis as well as all analyses of responder/survivor proportion endpoints performed on ITT and PP population, patients who do not provide data for the responder/survivor endpoint will be considered non-responders/censor, i.e., assigned to the less favorable outcome for the endpoint.

Sensitivity analyses to assess the robustness of conclusions to missing data will be carried out if there are more than 5% of patients missing evaluations in either treatment arm. Sensitivity analyses will include an analysis that assumes that outcomes are missing at random.

- For imputing missing parts of dates for the efficacy analyses (except OS) the missing day in a date will be imputed as the 15th of the month, if month and year is documented. If the imputation is earlier than the date of randomization, the day of randomization is taken. In all other cases missing

or incomplete dates will not be imputed.

- For imputing missing day of death date, if month and year is available, the day will be imputed by 15, unless this results in a date not later as a date the subject is known to be alive. In that case the date of death will be imputed by the last date known to be alive + 1.

17. QUALITY OF LIFE ANALYSIS

NOT APPLICABLE.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF. There will be no statistical comparisons between the dosing cohorts for safety data.

18.1. ADVERSE EVENTS

A clinical study AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of medicinal (investigational) product, whether related to the medicinal (investigational) product. Relevant information is recorded on CRF page "Adverse Events".

AE Report period:

- From ICF signing to first study medication administration - All AEs related to the study procedures (eg, blood withdrawal etc.).
- From the start of the first study medication administration until 28 days after discontinuation/completion of the study medication or up to Week 53 after randomization - All AEs, regardless of relationship to the study medication/study procedures. During the LTE study, only adverse events of special interest (AESIs) and SAEs until 28 days after the subject's last dose will be collected.

All Treatment-Emergent Adverse Events (TEAEs) are defined as AEs that started or worsened on or after the first dose of study medication through 28 days after last dose.

Prior AEs are AEs that started or worsened (where a new record shall be reported) prior to the first dose of IMP. If for reasons such as partial/missing dates, it is not possible to define an AE as prior or treatment-emergent, it will be classified as a TEAE. All AEs other than prior AEs will be considered TEAEs.

When AE start date coincides with first dose date, relevant timing can be obtained by comparing infusion start time and AE start time. Where it is still not possible to classify an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the output templates.

For all SOC/PT summaries, all AEs will be presented in alphabetic order.

Listings will include TEAEs.

18.1.1. ALL TEAEs

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per subject, using MedDRA (latest version) PT as event category and MedDRA (latest version) SOC body term as Body System category.

Unless otherwise stated adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

If an adverse event is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.

Adverse events related to trial treatment are those events with relationship missing, unknown or CRF listed as possibly related and definitely related.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

An overview table of TEAEs will be provided detailing the number and percentage of subjects with:

- Any TEAE
- Any related TEAE
- Any BAT1706 related TEAE
- Any EU-Avastin related TEAE
- Any Carboplatin related TEAE
- Any Paclitaxel related TEAE
- Any serious TEAE
- Any related serious TEAE
- Any BAT1706 related serious TEAE
- Any EU-Avastin related serious TEAE
- Any Carboplatin related serious TEAE
- Any Paclitaxel related serious TEAE
- Any TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Trial treatment related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Treatment BAT1706 related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Treatment EU-Avastin related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Treatment Carboplatin related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Treatment Paclitaxel related TEAE by NCI-CTCAE severity grade (≥3, ≥4)
- Any TEAE leading to death
- Any related TEAE leading to death
- Any BAT1706 related TEAE leading to death
- Any EU-Avastin related TEAE leading to death
- Any Carboplatin related TEAE leading to death

- Any Paclitaxel related TEAE leading to death

The following summary tables will also be provided for TEAEs detailing the number and percentage of subjects by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically):

- TEAEs
- Trial drug related TEAEs
- Non-serious TEAEs at a frequency threshold of 5% (Events that occurred at least among 5% of subjects)
- TEAEs by worst grade (for each subject, maximal grade within the same preferred term)
- Trial drug related by worst grade
- Grade ≥3 TEAEs
- Grade ≥3 related TEAEs
- BAT1706 Grade ≥3related TEAEs
- EU-Avastin Grade ≥3 related TEAEs
- Carboplatin Grade ≥3 related TEAEs
- Paclitaxel Grade ≥3 related TEAEs
- TEAEs leading to death
- Trial drug related TEAEs leading to death
- BAT1706 related TEAEs leading to death
- EU-Avastin related TEAEs leading to death
- Carboplatin related TEAEs leading to death
- Paclitaxel related TEAEs leading to death

All TEAEs will be listed to support these tables. A listing of TEAEs leading to death will also be provided including all relevant information.

18.1.1.1. Severity

The severity of all TEAEs will be graded according to 5 grades (Grade 1 to Grade 5) in accordance with the national cancer institute common terminology criteria for adverse event (NCI-CTCAE) V4.03.

TEAEs starting with a missing severity will be treated as missing severity and presented wherever applicable. Severity will be listed for TEAEs in the SAF.

18.1.1.2. Relationship to Study Medication

As indicated by the Investigator, causal relationship between AEs and study treatment is classed as “Definitely Related” “Possibly Related”, “Unlikely Related” or “Not Related”. TEAEs with a missing relationship to study medication will be regarded as “Definitely Related” to the question.

Incidence of related TEAEs will be presented by SOC and then PT. TEAEs of each causal relationship level will be listed.

18.1.2. TEAEs LEADING TO IMP DISCONTINUATION

TEAEs leading to permanent discontinuation of IMP will be identified according to the item "Action Taken with Investigational Product" on the "Adverse Events" form of the CRF, such as, "IP was permanently stopped due to this AE", etc.

TEAEs leading to IMP discontinuation will be listed.

18.1.3. SERIOUS TEAEs

A serious adverse event (SAE) is defined as any adverse event resulting in death, life-threatening, requires inpatient hospitalization (initial or prolonged), persistent or significant Disability/Incapacity, congenital anomaly or birth defect or any other important medical events

Detailed definition of SAEs can be found in protocol section 6.2.1.

On CRF, SAEs are those events with a response of "Yes" for the item "Serious". Summaries of incidence rates (frequencies and percentages) of serious TEAEs by SOC and PT will be prepared.

18.1.4. TREATMENT EMERGENT ADVERSE EVENTS OF SPECIAL INTEREST (TEAESI)

According to the mechanism of IMP, the TEAESI include following ⩾ Grade 2 renal, hepatic, cardiac and hematologic AEs:

- Hypertension >= Grade 3
- Proteinuria >= Grade 3
- Gastrointestinal perforation, gastrointestinal abscesses and gastrointestinal fistulae (any grade)
- Wound healing complications >= Grade 3
- Hemorrhage >=grade 3 (any grade CNS bleeding; >= Grade 2 haemoptysis)
- Arterial thromboembolic events (anygrade)
- Venous thromboembolic events >= Grade 3
- Posterior reversible encephalopathy syndrome (any grade)
- Chronic heart failure >= Grade 3
- Non-gastrointestinal fistula or abscess >= Grade 2

Protocol section 6.2.1.1 provides a detailed description of all AESIs.

TEAESI can be identified on the "Adverse Events" CRF page with question "Is this an Adverse Events of Special Interest (AESIs)?" Summaries of incidence rates (frequencies and percentages) of TEAESIs by SOC and PT will be prepared.

18.2. DEATHS

All deaths, deaths within 30 days after last dose of study treatment (BAT1706, EU-Avastin, carboplatin, or paclitaxel), deaths within 60 days after first dose of study treatment (BAT1706, EU-Avastin, carboplatin, or paclitaxel) as well as the primary reason for death, will be tabulated based on information from the "Report on Death" CRF page:

- Any subject who died and primary reason for death
  - Progressive disease and/or disease related condition
  - Related to study treatment(s)
    - BAT1706
    - EU-Avastin
    - Carboplatin
    - Paclitaxel
  - Event unrelated to study treatment
  - Unknown
- Subjects who died within 30 days after last dose of treatment and primary reason for death
  - Progressive disease and/or disease related condition
  - Related to study treatment(s)
    - BAT1706
    - EU-Avastin
    - Carboplatin
    - Paclitaxel
  - Event unrelated to study treatment
  - Unknown
- Subjects who died within 60 days after first dose of treatment and primary reason for death
  - Progressive disease and/or disease related condition
  - Related to study treatment(s)
    - BAT1706
    - EU-Avastin
    - Carboplatin
    - Paclitaxel
  - Event unrelated to study treatment
  - Unknown

In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information (date of first / last administration, separately for cetuximab, cisplatin, carboplatin, and 5-FU).
This listing will also include:

- Data from “Report on Death” CRF page
- Flag for death within 30 days after last dose of trial treatment (BAT1706, EU-Avastin, carboplatin, or paclitaxel)
- Flag for death within 60 days after first dose of trial treatment (BAT1706, EU-Avastin, carboplatin, or paclitaxel)

18.3. LABORATORY EVALUATIONS

Laboratory samples will be analyzed at the study site's local laboratory. Laboratory assessments will include the following:

- **Hematology:** Hemoglobin, Hematocrit, Platelets, White Blood Cell, Lymphocytes, Neutrophils (recorded on CRF page "Hematology")
- **Chemistry:** Creatinine, AST, ALT, ALP, Gamma-Glutamyl Transpeptidase, Total Bilirubin, Direct Bilirubin, Glucose, Total Cholesterol, Total Protein, Albumin, Sodium, Potassium, Chloride, Calcium. (recorded on CRF page "Chemistry")
- **Coagulation:** INR, aPTT, PT. (recorded on CRF page "Coagulation"). Coagulation data will be presented together with hematology records.
- **Serology:** Test results for Hepatitis B Virus (HBV) antigen, Hepatitis B Virus (HBV) antibody, Hepatitis C Virus (HCV) antibody, Human Immunodeficiency Virus (HIV) will be summarized in terms of number of subject being positive/negative. A listing will also be provided.
- **Urinalysis**: Recorded on CRF page "Urinalysis".
- **24 hours urine test:** Urine protein and creatinine ratio (UPCR), which are captured on CRF page "24-hour Urine Test", will be summarized together with serum chemistry.
- **Pregnancy test**: For females of child-bearing potential only: Human Chorionic Gonadotropin in serum and urine Recorded on CRF page "Serum Pregnancy Test".

Test normal ranges of all quantitative tests above, if applicable, are also recorded in the EDC system.

Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of normal range (LLN), or "> X", i.e. above the upper limit of normal range (ULN), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

For Hematology, Coagulation, and Chemistry parameters that are CTCAE gradable, shift tables of baseline CTCAE grade versus the worst CTCAE grade will be presented. Unscheduled measurements will be included in summaries.

Changes over time will be described using descriptive statistics, and the percentage of subjects with values outside the normal range will be presented.

For Urinalysis parameters, actual value of each scheduled visit, change from baseline for each post-baseline scheduled measurement will be presented by visit.

NCI-CTCAE grades available:

The laboratory toxicities will be tabulated by the worst on-treatment CTCAE grade or the shift of CTCAE grade from baseline to worst grade during on-treatment period using descriptive statistics (count and percentage). The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

• The worst grade during the on-treatment period will be summarized considering only patients with post baseline laboratory samples: Laboratory tests by NCI-CTCAE grade (0, 1, 2, 3, 4, and missing).

The shift table will summarize baseline CTCAE grade vs. the worst on-treatment CTCAE grade (grade = 0, 1, 2, 3, 4, missing). The above analyses apply to the following hematology and biochemistry parameters which can be graded per NCI-CTCAE (Appendix 4):

- **Hematology** – Hemoglobin, Platelet, White Blood Cells, Neutrophils (Absolute), Lymphocytes (Absolute)

- **Chemistry** – Albumin, Alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total Bilirubin, Calcium, Glucose, Potassium, Sodium, Creatinine, Gamma-Glutamyl Transpeptidase.

Tables will summarize, separately for hematology and biochemistry parameters, the shift from baseline grade to worst on-treatment grade by parameters and treatment group.

NCI-CTCAE grades not available:

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

The worst on-treatment value for hematology and biochemistry parameters which cannot be graded per NCI-CTCAE will be summarized by parameter according to the local laboratories normal ranges as follows:

- Shift from baseline value (low, normal, high) to above normal during on-treatment period

Shift from baseline value (low, normal, high) to below normal during on-treatment period. The above analyses apply to the following hematology and biochemistry parameters which cannot be graded per NCI-CTCAE:

- **Hematology:** Red Blood Cells, Monocytes, Eosinophils, Basophils.
- **Biochemistry:** Direct Bilirubin, Total Protein, Chloride.

All parameters will be listed with abnormality and CTCAE grade for SAF when applicable.

18.4. ECG EVALUATIONS

The following measurements will be presented and listed for SAF, and change from baseline will be prepared for quantitative parameters:

- Heart Rate (beats/min)
- RR Interval (msec)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) – corrected by Fridericia method
- Overall ECG evaluation
    - Abnormal, clinical significance
    - Abnormal, not clinical significance
    - Normal

Conclusions are sorted as Normal/Abnormal non-clinically significant/Abnormal clinically significant, the latest one being considered as the worst. If no post-baseline data are available, the worst on-treatment result will be accounted as missing. If significance is not provided, the conclusion will be classified as “Abnormal ECG”. This “Abnormal ECG” category will count abnormal conclusion with missing significance only. A listing of all ECG parameters results will be provided.

18.5. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Body Temperature (^{o}C)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)

The following summaries will be provided for vital signs data: Actual and change from baseline by visit

18.6. PHYSICAL EXAMINATION

The following physical examination and neurological examination will be reported for this study:

- Height (cm)
- Weight (kg)
- General appearance
- Abdomen
- HEENT (Head, Eyes, Ears, Nose and Throat)
- Neck
- Chest/Respiratory
- Heart/Cardiovascular
- Gastrointestinal/Liver
- Musculoskeletal/Extremities
- Skin
- Thyroid/Neck
- Lymph Nodes
- Neurological/Psychiatric

The summaries of examination results will be provided in listing.

18.7. IMMUNOGENICITY ASSESSMENTS

Samples collected for immunogenicity assessments will initially be screened for antidrug antibodies (ADA) against the IMP. A confirmation assay will be used to confirm the positive status for samples which scored potentially positivity by the screening assay. In confirmed positive samples, the relative titer of the antibody will be determined as well as whether the confirmed positive sample represent a neutralizing antibody. A neutralizing ADA assay will be performed on the confirmed positive samples.

Immunogenicity results including overall ADA results (screening, confirmatory and titers, as appropriate), neutralizing ADA results.

The immunogenicity results will be listed for anti-drug antibodies and neutralizing antibodies for each patient

and time point (CRF: "ADA/NADA Blood Samples").

- ADA/NADA Status
  - Positive
  - Negative
  - Unknown

18.8. ECOG PERFORMANCE

The Eastern Cooperative Oncology Group/ECOG performance status of each subject will be reviewed at the time points outlined in the Table 1 of protocol. Shifts in ECOG performance status from baseline to worst on-treatment performance status will be summarized by treatment group. Missing category will also be included (CRF" ECOG Performance Status"). A listing will also be provided for ECOG performance status.

19. GENETIC ANALYSIS

NOT APPLICABLE.

20. DATA NOT SUMMARIZED OR PRESENTED

NOT APPLICABLE.

21. PHARMACOKINETIC ANALYSIS

21.1. PRECISION

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters (if any) will be rounded for reporting purposes in by-subject listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters, if determined, directly derived from source data (eg Cmin) will be reported and analyzed with the same precision as the source data.
- Parameters, if determined, derived from actual elapsed sample collection times (eg, tmax) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the mean, standard deviation, standard error, and CIs will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Ratios of means for PK parameters will be presented with two decimal places (as a percentage) to meet regulatory requirements and P-values, if any, shall be reported to four decimal places or as <0.0001.

21.2. CONCENTRATION DATA

A descriptive comparison of bevacizumab concentrations between treatments will be used to evaluate the

secondary objective.

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable inclusion in descriptive statistics summaries. Missing concentrations will be treated as missing.

A listing of PK blood sample collection times as well as derived sampling time deviations (typically relative to the infusion start time, end time where called for based on the nominal description of the sampling timepoint) will be provided. Plasma concentrations will be summarized using descriptive statistics by treatment. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. If average concentrations are BLQ, they will be presented as 0 or LLOQ.

A subject listing of all concentration-time data for each treatment will be presented. Figures of arithmetic mean concentration-time data (± STD, as appropriate) will be presented by treatment on linear and semi-logarithmic scales. Individual subject concentration-time data will be graphically presented on linear and semi-logarithmic scales.

21.3. PHARMACOKINETIC PARAMETERS

Given the morbidity of patients with advanced lung cancer, the post dose blood sampling profile for Cycle 1 and Cycle 6 is limited and missing data and out of window sampling is anticipated; therefore, no traditional PK parameter determination using noncompartmental analysis is planned. However, PK parameters (e.g., AUC, maximum concentration, and time to maximum concentration) may be determined to if the data allow if appropriate.

21.4. EXPOSURE RESPONSE CORRELATION

Data from this study could be used to support future exploratory population PK modelling and/or correlation analysis if warranted to interpret the data. If performed, a separate analysis plan will be prepared, and results will be reported separately from the clinical study report.

22. REFERENCES

Protocol version 5.0,20Jun2019.

BAT1706-003-CR CRF Version 05 - Annotated Trial Design, Dated 12Mar2019.

BAT1706-003-CR CRF Version 05 - Unique Form, Dated 12Mar2019.

23. APPENDICES

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

- **IQVIA Output Conventions**

Outputs will be presented according to the IQVIA's general guidelines and template for outputs conventions.

- **General Rules**

The following conventions will be applied for reporting descriptive statistics of all continuous data (except PK values):

Mean, Median, Q1, Q3, Minimum, and Maximum will have the same precision as SDTM data (number of digits) for non-derived data (e.g. weight).

SD will be presented with one digit more than mean.

Statistics on derived data (e.g. treatment exposure time in days) will be rounded to reasonable number of digits. Maximal digits should be available in ADaM datasets.

Qualitative variables will be summarized by counts and percentages. A missing category should always be displayed at baseline – even when there are no missing data. A missing category, at other endpoints than baseline, should only be displayed when there are missing data. Unless otherwise stated, the calculation of proportions will be based on the number of subjects of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Total of missing and non-missing observations at each time-point will reflect the population still in the trial at that time. For example, if a subject is still in the trial at the time-point but with missing data, it should be counted in the number of missing observations.

- **Dates & Times**

Depending on data available, dates and times will take the form DDMMMYYYY and HH:MM:SS.

- **Spelling Format**

English US

- **Presentation of Treatment Groups**

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment arm
- Center-subject ID
- Date (where applicable)

All tables containing coded terms (CM, MH, AE, etc), coded records will be sorted in alphabetic order.

APPENDIX 2. PARTIAL DATE CONVENTIONS

- **Algorithm for Treatment Emergence of Adverse Events:**

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date and start date<=study med stops date +28 days, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date and start date<=study med stops date +28 days, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date and start date<=study med stops date +28 days, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

- **Algorithm for Prior / Concomitant Medications/Concomitant procedures:**

START DATE	STOP DATE	ACTION
Known	Known	If stop date < the time of signing informed consent , assign as prior If stop date >= the time of signing informed consent and start date <= end of treatment +28 days, assign as concomitant If stop date >= the time of signing informed consent and start date > end of treatment + 28 days, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown),then: If stop date < the time of signing informed consent, assign as prior If stop date >= the time of signing informed consent and start date <= end of treatment + 28 days, assign as concomitant If stop date >= the time of signing informed consent and start date > end of treatment + 28 days, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 28 days, assign as concomitant If start date > end of treatment + 28 days, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < the time of signing informed consent, assign as prior If stop date >= the time of signing informed consent and start date <= end of treatment + 28 days, assign as concomitant If stop date >= the time of signing informed consent and start date > end of treatment + 28 days, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < the time of signing informed consent, assign as prior If stop date >= the time of signing informed consent and start date <= end of treatment + 28 days, assign as concomitant If stop date >= the time of signing informed consent and start date > end of treatment + 28 days, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 28 days, assign as concomitant If start date > end of treatment + 28 days, assign as post treatment
Missing	Known	If stop date < the time of signing informed consent, assign as prior If stop date >= the time of signing informed consent, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown),then: If stop date < the time of signing informed consent, assign as prior If stop date >= the time of signing informed consent, assign as concomitant Cannot be assigned as 'post treatment'

START DATE	STOP DATE	ACTION
	Missing	Assign as concomitant

APPENDIX 3. CONFIRMATION OF BEST OVERALL RESPONSE

Initial overall response	Subsequent overall response	Confirmed time point overall response
CR	CR	CR provided subsequent CR is ≥ 28 days away from the first timepoint
CR	PR	SD provided minimum criteria for SD duration met; otherwise, PD
CR	SD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met; otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR provided subsequent CR is ≥ 28 days away from the first timepoint
PR	PR	PR provided subsequent PR is ≥ 28 days away from the first timepoint
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
SD	Any	SD provided minimum criteria for SD duration met, otherwise, NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PD	Any	PD
NE	NE	NE

Footnote:

(a) CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

(b) CR and PR need to be confirmed by subsequent tumor assessment at least 28 days later.

(c) SD minimum evaluation interval will be at least 35 days.

(d) If a subject only has a response value of NE or the only response value is SD and is within 36 days of the first administration date, the best response will be NE.

APPENDIX 4. CTCAE V4.03 GRADE OF HEMATOLOGY AND CHEMISTRY

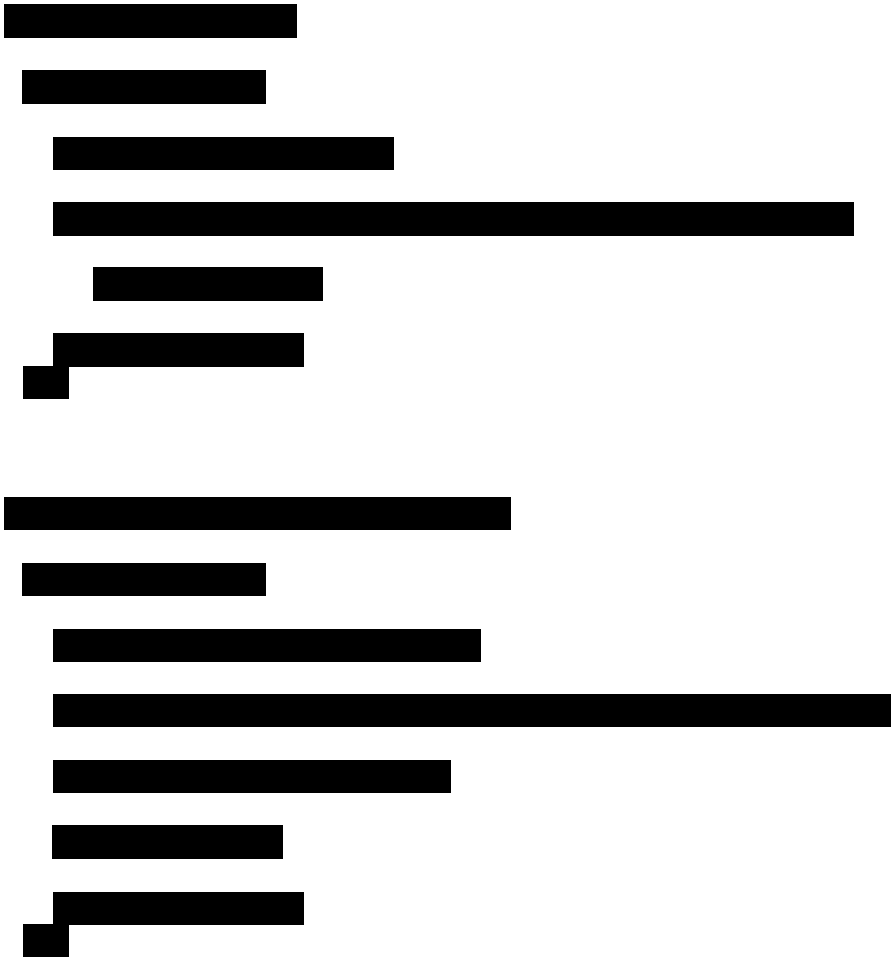
Lab Test Name	Direction toxicity	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology								
Hemoglobin - Low	Decrease	Blood and lymphatic system disorders	Anemia	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin - High	Increase	Investigations	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Leukocytes/ White blood cell	Decrease	Investigations	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Lymphocyte - Low	Decrease	Investigations	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Lymphocyte - High	Increase	Investigations	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Neutrophils	Decrease	Investigations	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Platelet count (PLT)	Decrease	Investigations	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Lab Test Name	Direction toxicity	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Chemistry								
Albumin	Decrease	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase (ALP)	Increase	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Alanine aminotransferase (ALT)	Increase	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate aminotransferase (AST)	Increase	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Total Bilirubin	Increase	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Creatinine	Increase	Investigations	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Potassium - Low	Decrease	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Potassium - High	Increase	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Sodium - Low	Decrease	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death

Lab Test Name	Direction toxicity	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium - High	Increase	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Calcium - Low	Decrease	Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Calcium - High	Increase	Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Glucose - Low	Decrease	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Glucose - High	Increase	Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Gamma glutamyl transferase	Increase	Investigations	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-

APPENDIX 5. SAMPLE CODE FOR EFFICACY ANALYSIS

[redacted]



[redacted]

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