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Affimed GmbH

STATISTICAL ANALYSIS PLAN

PROTOCOL AFM24-102

A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of AFM24 in Combination with Atezolizumab in Patients with Selected Advanced/Metastatic EGFR-expressing Cancers

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APPROVAL SIGNATURES

STUDY TITLE: A Phase 1/2a Open Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of AFM24 in Combination with Atezolizumab in Patients with Selected Advanced/Metastatic EGFR-expressing Cancers

PROTOCOL NUMBER: AFM24-102

SAP Final 2.0, 22 July 2024

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ADA	Anti-drug Antibodies
CBR	Clinical Benefit Rate
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DDS	Dose-determining set
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
FAS	Full Analysis Set
GEJ	gastro-esophageal junction
i.v.	Intravenously
IA	Interim Analysis
IDMC	Independent Data Monitoring Commitee
IFN-α	Interferon alpha
IFN-β	Interferon beta
IRR	Infusion-related Reaction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NK	Natural Killer
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
qw	once weekly
q2w	once every 2 weeks
RP2D	Recommended Phase 2 Dose
RECIST	Response Evaluate Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TNF-α	Tumor Necrosis Factor-alpha

WHO	World Health Organization
WT	wild type

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis and reporting for the study protocol AFM24-102 (version 4.0) dated 10 May 2023. It is based on the final electronic case report forms (eCRFs) v5.0 dated 13JUL2023.

3. STUDY OBJECTIVES

3.1 PHASE 1 (DOSE ESCALATION)

3.1.1 PRIMARY OBJECTIVE

To determine the maximum tolerated dose (MTD) and/or to select one or more recommended phase 2 doses (RP2Ds) of AFM24 in combination with atezolizumab.

3.1.2 SECONDARY OBJECTIVES

- To assess the safety and tolerability of AFM24 in combination with atezolizumab
- To evaluate the preliminary antitumor activity of AFM24 in combination with atezolizumab in terms of objective response rate (ORR)
- To characterize the pharmacokinetic (PK) profile of AFM24 when AFM24 is given in combination with atezolizumab
- To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab

3.1.3 EXPLORATORY OBJECTIVES

- [redacted]

3.2 PHASE 2A (EXPANSION)

3.2.1 PRIMARY OBJECTIVE

To evaluate the antitumor activity of AFM24 in combination with atezolizumab in terms of ORR.

3.2.2 SECONDARY OBJECTIVES

- To assess preliminary efficacy of AFM24 in combination with atezolizumab using additional measures of clinical benefit
- To assess the safety and tolerability of AFM24 in combination with atezolizumab
- To characterize the PK profile of AFM24 when AFM24 is given in combination with atezolizumab

- To assess the immunogenicity of AFM24 when AFM24 is given in combination with atezolizumab

3.2.3 EXPLORATORY OBJECTIVES

- [redacted]

4. STUDY DESCRIPTION

4.1 OVERALL STUDY DESIGN

AFM24-102 is a Phase 1/2a open label, non-randomized, multicenter, dose escalation and expansion study evaluating AFM24 in combination with atezolizumab (investigational treatment: AFM24 + atezolizumab) in patients with select epidermal growth factor receptor (EGFR)-expressing advanced solid malignancies whose disease has progressed after treatment with previous anti-cancer therapies.

There will be 2 parts in this study: a dose escalation phase (Phase 1) and an expansion phase (Phase 2a). Patients will qualify to receive the investigational treatment (AFM24 + atezolizumab) in the dose escalation phase (Phase 1) or in the expansion phase (Phase 2a) only if they are deemed eligible post the safety lead-in phase where they will receive a single intravenous (i.v.) AFM24 infusion. Patients who qualify for the safety-lead in phase will receive AFM24 i.v. infusion, once weekly (qw), in 4-week cycles and atezolizumab i.v. infusion, once every 2 weeks (q2w), in 4-week cycles.

The full study scheme can be seen in the Protocol section 4.1.

4.2 SAFETY LEAD-IN PHASE

Seven days prior to Cycle 1 Day 1 (C1D1) (i.e., at Day -7 [minus 7]), patients will receive a single dose of AFM24 (dose assigned to a given cohort) and will be observed for any Adverse Event (AE) for 1 week (from Day -7 through Day -1 the safety lead-in phase). Patients who have any Grade ≥3 cytokine release syndrome (CRS) or infusion-related reaction (IRR) symptoms lasting >6 hours or any other possibly related Grade ≥3 non-hematological Treatment-Emergent Adverse Events (TEAE) or clinically significant hematological Grade ≥3 TEAEs during their safety lead-in phase will be permanently discontinued from the study. Patients not proceeding to combination therapy (AFM24 + atezolizumab) will be replaced.

4.3 PHASE 1

The aim of the dose escalation phase (Phase 1) is to determine the MTD/RP2D of AFM24 in

combination with atezolizumab.

The 160 mg i.v. qw dose was selected as the starting dose for the AFM24-102 study, based on the data obtained from the first in human study (AFM24-101). There were 2 additional dose escalations completed for AFM24, where the dose increase was based on data from the AFM24-101 study, in conjunction with the safety and PK data emerging from this study (see Protocol Section 2.4). Dose increases did not exceed 200% of the current dose. All dose escalation (and de-escalation) decisions were determined by the Safety Review Committee (SRC).

4.4 PHASE 2A

Once all patients completed Cycle 1 of the dose escalation phase (Phase 1), the SRC reviewed all available safety, clinical, laboratory, and PK data and recommended continuing with the phase 2 portion of the study. The RP2d of AFM24 in combination with atezolizumab was determined. The MTD was not reached. Enrollment into the expansion cohorts for the selected cancer indications in the expansion phase (Phase 2a) began (see Protocol Section **Error! Reference source not found.**).

A Simon two-stage optimal design will be utilized for Expansion Cohorts 1 and 2. Expansion Cohorts 3 and 4 are exploratory with no hypothesis testing. The expansion phase (Phase 2a) of the study is intended to collect preliminary evidence of efficacy and to further confirm the safety of AFM24 in combination with atezolizumab.

During the expansion phase (Phase 2a), up to 130 patients will receive weekly infusions of AFM24 at the RP2D in combination with an every two-week infusion of atezolizumab in four-week cycles in four expansion phase cohorts based on tumor types.

Based on results from dose-escalation phase (Phase 1), additional treatment schedules of AFM24 administration (i.e., q2w) may be explored as part of the expansion phase (Phase 2a) within or across cohorts.

Patients will receive the investigational treatment (AFM24 + atezolizumab) until disease progression, intolerable toxicity, at the investigator's discretion, or patient withdrawal of consent.

4.5 REPLACEMENT OF PATIENTS

In Phase 1 (dose escalation), a patient who did not fulfill the Dose Limiting Toxicity (DLT) requirements (refer to the protocol section **Error! Reference source not found.**) and who discontinued study participation prior to completing the DLT observation period due to any reason other than a DLT, would be replaced for DLT evaluation but will remain in the Safety Analysis Set (see Section 7.1 for definition).

For the dose escalation (Phase 1) and expansion phase (Phase 2a), all patients who begin AFM24 treatment (e.g. Day -7) but discontinue prior to receiving any amount of atezolizumab will be replaced but will remain in the overall Safety Analysis Set. A replacement patient will be enrolled and assigned the same cohort or dose level.

4.6 STUDY TREATMENT

AFM24 will be administered as an i.v. infusion, qw (or q2w as part of the Phase 2a in case

additional treatment schedules of AFM24 administration are explored), in 4-week cycles.
Atezolizumab will be administered as i.v. infusion, q2w, in 4-week cycles.
Refer to the Pharmacy Manual for full details regarding study drug administration.

4.6.1 PHASE 1 TREATMENT ASSIGNMENT AND SCHEDULE

For the dose escalation phase (Phase 1), patients received AFM24 and atezolizumab in an open label fashion according to the following treatment schedule for their assigned cohort:

- Cohort 1 (N= 4)
  160 mg AFM24 i.v. qw + Atezolizumab 840 mg i.v. q2w
- Cohort 2 (N= 6)
  480 mg AFM24 i.v. qw + Atezolizumab 840 mg i.v. q2w

4.6.2 PHASE 2A TREATMENT SCHEDULE

Patients who are remain eligible post-evaluation for AFM24-hypersensitivity during the safety-lead in phase (Day -7 through Day -1) will receive the investigational treatment (AFM24 + atezolizumab) as per the following regimens, with the RP2D defined as 480 mg:

- EXP-1 (EGFR-wild type (WT) Non-small cell lung cancer (NSCLC)):
  AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-2 (gastric or gastro-esophageal junction [GEJ] adenocarcinoma):
  AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-3 (Hepatocellular Carcinoma, Hepatobiliary-, or Pancreatic Adenocarcinoma):
  RP2D AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w
- EXP-4 (advanced or metastatic NSCLC harboring a targetable EGFR kinase domain mutation): RP2D AFM24 i.v. qw or q2w at RP2D dose + Atezolizumab 840 mg i.v. q2w

Additional treatment schedules of AFM24 administration (e.g., every 2 weeks) may be explored as part of the Phase 2a within or across cohorts.

4.7 SAFETY REVIEW COMMITTEE (SRC)

The SRC convened to make a decision on the dose escalation in the Phase 1.

All details regarding the SRC composition, meetings, reviewed data and the decision-making process will be documented in the study-specific SRC Charter.

4.8 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The IDMC, consisting of clinical experts who are not directly involved in this clinical study, will be established for the Phase 2a of the study. The IDMC will review all safety data generated throughout the dose expansion phase (Phase 2a) of the study on a regular basis. Based on the outcome of their review, the IDMC will provide recommendations to the Sponsor with regard to study conduct or study procedures. The set-up and operational process for this IDMC will be described in a separate IDMC charter.

5. SAMPLE SIZE AND POWER CALCULATION

Please refer to the protocol section 9.1 for sample size justifications.

6. ANALYSIS ENDPOINTS

Please refer to the protocol section 3 for Objectives and Endpoints.

7. ANALYSIS POPULATIONS

7.1 SAFETY ANALYSIS SET

The Safety Analysis Set will consist of all patients who received at least any amount of AFM24 or atezolizumab. The Safety Analysis Set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

7.2 FULL ANALYSIS SET (FAS)

The FAS will consist of all patients who received at least any amount of both AFM24 and atezolizumab. The FAS will be the primary population for all efficacy related endpoints.

7.3 DOSE-DETERMINING SET (DDS)

The DDS will consist of all patients in the Safety Analysis Set, who have either (a) experienced DLT at any time during Cycle 1, or (b) met the minimum safety evaluation requirements without experiencing DLT within Cycle 1.

Patients must receive ≥ 75% of their assigned AFM24 dose in Cycle 1, receive ≥ 50% of their assigned atezolizumab dose in Cycle 1, complete the 28-day DLT observation period and have at least one post-baseline assessment of the following safety parameters: Physical Examination, Vital Signs, Laboratory, and Electrocardiogram (ECG), or have had a DLT within the first cycle of treatment to be considered evaluable for DLT.

7.4 PK SET

The PK set consists of all patients who have received at least 1 adequately documented dose of AFM24 and have at least 1 adequately documented post dose PK measurement.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All analyses will be performed using SAS® statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]).

Descriptive statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, and maximum values. All raw data will be presented to the original number of decimal places. Means, medians, and confidence intervals will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data. Summary statistics for categorical variables will contain count and percentage. Percentages will be presented to one decimal, except for one hundred percent, which will be presented as 100%. Unless otherwise specified, percentages for baseline summaries will be based on the total number of patients in the treatment arm or

overall, for the indicated population (dependent on table column heading), percentages for post-baseline summaries will be based on the total number of patients with non-missing values in the treatment arm or overall.

Change from Baseline at Visit X is defined as Test Value at Visit X – Baseline Value.

Unless otherwise stated, all analyses will be descriptive in nature, no formal statistical comparisons of data from different arms or cancer type will be done.

Data will be listed individually by patient.

The tables and the listings will be done separately for two phases. Phase 1 summaries will be presented by the dose level, and Phase 2a summaries by Expansion Cohort.

8.2 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Baseline is defined as the last non-missing observation prior to the first dose of either AFM24 or atezolizumab (screening assessment for most of the parameters, or Day -7 pre-dose, where applicable).

Data will be analyzed in accordance with the visits recorded in the eCRF. No visit reassignment will be done.

Time points for analysis of vital signs will be assigned using protocol-defined windows (refer to Protocol section 8.2.4 table 3).

Handling of Missing Data

[redacted]

8.3 PATIENT DISPOSITION

Total number of patients screened, enrolled and failed screening will be summarized on all screened patients, together with reasons for the screen failure; country of enrolled patients will also be summarized. All patients who have signed the informed consent form are considered

screened; enrolled refers to the eCRF field called “Was Subject enrolled in the study?”. Number of patients included in each analysis set and reasons for study discontinuation will also be summarized. Summaries will be done for all enrolled patients, DDS for Phase 1, and for all enrolled patients and Safety Analysis Set for Phase 2a.

Listings of all screened patients, reasons for screen failure, study populations, and inclusion/exclusion criteria not met will be created. Study discontinuation data will also be listed.

8.4 PROTOCOL DEVIATIONS

Protocol Deviations will be summarized by counts and percentages. Major important, major and minor deviations will be summarized separately. Rules for identifying and treating protocol deviations are described in the Protocol Deviations Management Plan. Summaries will be done for all enrolled patients. A listing of all protocol deviations, along with their grade as major important, major or minor, will be provided for all screened patients.

8.5 PATIENT CHARACTERISTICS

All summaries in this section will be done for both Safety Analysis Set and FAS for Phase 1 and Phase 2a.

8.5.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Following characteristics at Baseline will be summarized for the Safety Analysis Set and the FAS:

- Age (years)
- Sex
- Female with childbearing potential (and a reason, if not)
- Race and Ethnicity
- Height
- Weight
- Pulmonary Function test

Smoking history (smoking status, smoking duration in years, number of cigarettes per day and number of years since quitting) and alcohol consumption will be summarized and listed with the demographic characteristics as well.

Listings of the baseline demography data will be prepared for the Safety Analysis Set.

8.5.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Prior Cancer History (Cancer Type, Cancer Stage, Histopathological Type, Extent at Screening, Location of Metastases, Gene Alteration / Protein Overexpression) together with the screening Eastern Cooperative Oncology Group (ECOG) performance status value will be summarized.

Listings of Cancer History data will be created.

Prior and Concurrent medical conditions other than cancer will also be summarized. All conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. Summaries will be split by System Organ Class (SOC) and Preferred Term (PT). A condition will be considered prior if its end date is prior to the first date of the study

drug administration. A condition will be considered concurrent if its end date is equal to or greater than the first date of the study drug administration.

Separate listings for Prior and Concurrent conditions will be created.

8.5.3 Prior and Concomitant Medications and Procedures

Prior Cancer Related Surgeries (number of surgeries and residual disease), Cancer Related Radiotherapy (number of radiotherapies and total dose) and Prior Cancer Therapy (number of regimens, regimen type, number of cycles, best response, reason for treatment discontinuation and coded therapy term) for cancer will be summarized. Numbers of prior surgeries and prior lines of treatment are calculated as the number of unique lines recorded on the respective eCRF page. Prior Cancer Therapies will be coded using World Health Organization (WHO) Drug Dictionary from March 2019.

Prior and Concomitant Medications will also be coded according to WHO Drug Dictionary from March 2019. They will be summarized by counts and percentages splitting by ATC2 and ATC4. Medications will be considered prior if the end date is prior to the first date of the study drug administration. A medication will be considered concomitant if its end date is equal to or greater than the first date of the study drug administration.

Separate listings will be created for Prior Cancer Related Surgeries, Radiotherapy Treatments and Therapies, and also for prior and concomitant medications. In addition, listings of Surgeries and other Procedures and Post-Study Anti-Cancer Treatment will be created.

8.6 Primary and Efficacy Endpoints and Analysis

All the efficacy tables will be run for Full Analysis Set for Phase 1 and for Phase 2a. Where specified additionally, sensitivity analyses on DDS will be run.

8.6.1 Analysis of Primary Endpoint

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8.6.2 ANALYSIS OF SECONDARY ENDPOINTS

Phase 1 (Dose Escalation)

Non-compartmental analysis will be conducted using concentration time data of AFM24. In addition, a population PK analysis may be conducted. Separate PK analysis plan(s) will be created as applicable, and results will be presented in separate PK report(s). As a part of the analysis described in this SAP, by time point summaries of PK concentration data will be created, grouped by dose level. Plots for individual PK concentrations will be generated as well. PK concentrations will be listed.

Anti-drug Antibodies (ADA) results (both screening and confirmatory results as well as titer) will be summarized by visit and change from baseline to worst-post-baseline. Listing of ADA data

will be created. The Immunogenicity data will be summarized for the Safety Analysis Set in Phase 1.

The ORR (CR or PR), Disease Control Rate (DCR) [CR or PR or stable disease (SD)] and Clinical Benefit Rate (CBR) [CR or PR or SD ≥24 weeks], assessed by the investigators using RECIST 1.1 will be summarized. Best overall response will be used to define the ORR, DCR and CBR. Best response is defined as the best observed response (CR>PR>SD>PD) throughout the study. See SAP Table 1 for rules of response confirmation. Summaries will include the count and percentages of different best overall responses, ORR, DCR and CBR for each dose level. The percentages will be based on the total number of patients in the Full Analysis Set for a given dose level.

In addition, waterfall plots for percentage change from baseline for sum of longest diameter and swimmer plots showing timing and results of RECIST 1.1 response assessments will be prepared. Waterfall plots will only include tumor assessments that were done at least 42 days after C1D1.

Phase 2a (Expansion)

[redacted]

[redacted]

The ORR (CR or PR), DCR (CR or PR or SD) and CBR (CR or PR or SD ≥24 weeks) assessed by the investigators using RECIST 1.1 will be summarized. The best overall response will be used to define the ORR, DCR and CBR. Best response is defined as the best observed response (CR>PR>SD>PD) throughout the study. See SAP table 1 for rules of response confirmation. Summaries will include the count and percentages and the 95% confidence intervals where appropriate of different best overall responses, ORR, DCR and CBR for each dose level. The percentages will be based on the total number of patients in the Full Analysis Set for a given Expansion Arm.

Waterfall and swimmer plots will also be created, similar to what is described for Phase 1, but additionally color coding of the Best Overall Response.

PK and ADA results matching Phase 1 secondary endpoints will be analyzed, but the presentation will be done by Expansion Cohort rather than by dose level. Analysis of Adverse Events is described in section 8.7.2.

8.6.3 Analysis of Exploratory Efficacy Endpoints and Additional Assessments

Phase 1 (Dose Escalation)

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Frequency of patients developing neutralizing ADAs against AFM24 will be summarized.

Lymphocyte subset counts, including number of total and activated Natural Killer (NK) cells and macrophages, will be summarized by descriptive statistics at each visit for each dose level. Listing of Lymphocyte subset counts and NK cells will be created as a part of the laboratory listings.

[redacted]

[redacted]

Phase 2a (Expansion)

The exploratory endpoints and assessments for Phase 2a match the ones for the Phase 1, excluding PFS and DOR. Similar analyses will be performed, but the presentation will be done by Expansion Arm rather than by dose level.

8.7 SAFETY ENDPOINTS AND ANALYSIS

Summaries for safety parameters will be done for the Safety Analysis Set for Phase 1 and Phase 2a. Tables will be presented by dose level for Phase 1 and by Expansion Arm for Phase 2a.

8.7.1 EXPOSURE TO STUDY TREATMENT

Total exposure to the AFM24 and Atezolizumab in mg will be summarized by visit and overall. Total Duration of Exposure to AFM24 and Atezolizumab in weeks, Delays, Interruptions and Dose Adjustments and reasons for those, overall number of cycles, Dose Intensity and Relative Dose Intensity will be summarized as well. Listings of AFM24 and Atezolizumab exposure data (doses and all dose adjustments) will be created.

[redacted]

Dose Intensity for AFM24 or Atezolizumab will be defined as the total amount of AFM24 or Atezolizumab respectively received by the subject in mg divided by the Duration of Exposure. Relative Dose Intensity will be calculated as the total dose of AFM24 or Atezolizumab received divided by the planned dose of AFM24 or Atezolizumab respectively per cycle times the number of initiated cycles.

The Exposure data will be summarized both for DDS and the Safety Analysis Set in Phase 1, and for Safety Analysis Set in Phase 2a.

8.7.2 ADVERSE EVENTS

Adverse Events will be summarized with patient counts, percentages and event counts by MedDRA SOCs and PTs. Following categories of AEs will be summarized: TEAEs, to study drugs related TEAEs, non-serious TEAEs, serious TEAEs and related serious TEAEs, TEAEs with NCI CTCAE Grades ≥3 and related TEAEs with NCI CTCAE Grades ≥3, TEAEs leading to premature discontinuation and interruptions, TEAEs and IRR at the day of the dosing or at the

next day, fatal TEAEs and related fatal TEAEs. An event will be considered study drug related if it has 'possibly', 'probably' or 'definitely' in relationship to study drug eCRF field.

Treatment-Emergent AEs, related TEAEs, serious TEAEs, related serious TEAEs, Grade 3/4/5 TEAEs, related Grade 3/4/5 TEAEs, TEAEs leading to study drug interruption or discontinuation presented by SOC and PT will also be summarized by maximum severity/CTC grade. For all TEAEs' summaries a number of patients with the event will be presented together with the total number of TEAEs.

[redacted]

A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, severity grade "4" will be imputed. If causality data is missing, 'Related to study medication' will be imputed.

Listings of AE data will be created.

Summaries of all deaths reported and deaths within 28 days after the last dose of study drug along with causes of death will be created. Listing of the death data will be created.

8.7.3 LABORATORY DATA

Safety laboratory results (Serum Chemistry, Hematology, Coagulation and Thyroid Function) will be graded by NCI CTCAE v5.0. If no grading exists, values will be classified into Low/Normal/High based on laboratory normal ranges. As only the local laboratory data are collected, no quantitative summaries of the laboratory data will be created. Urinalysis results will be summarized categorically.

For laboratory results reported with a "<" sign, half of the value that follows will be used for the analysis. Results reported after ">" sign will be analyzed as is.

Shift tables classified by reference range indicator (Low, Normal, and High) and also by CTCAE toxicity grades (worst toxicity grade in a period from the first dose until final visit, not including Follow-Up period) from baseline will be presented separately by laboratory test, where applicable.

All laboratory values will be listed. A separate listing for abnormal lab values (Grade 3 and higher, and low/high values) will be presented.

8.7.4 VITAL SIGNS AND OTHER SAFETY PARAMETERS

Vital signs will be summarized by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided.

Local-read ECG data will be listed overall and a separate listing for any clinically significant finding in ECG values will be provided. The frequency and percentage of patients with clinically significant ECGs will be tabulated as well.

Physical Examination data will be summarized by visit. Listing of the PE data will be created.

8.8 Exploratory Analysis

[redacted]

[redacted]

[redacted].

9. INTERIM ANALYSES

[redacted]

10. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The analysis of DCR by months 2, 6, 9, 12 and 15 is not appropriate and will be removed in the upcoming protocol amendment. Instead, the overall DCR is calculated and analyzed.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS© version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing/figure, the *company name and protocol number* will be presented. On the next line, an *output number* followed by the *title* of the table/listing/figure and p*opulation* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* and its location, *programmer ID*, the *name of the program output* and its location and *date of used data sets* will appear bottom left and the page number will appear on the top right corner of each table/listing. The *date and time of creation* of table/listing will appear top right just above the page number.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format; for example, 07MAY2002.

The list of tables, listings, and figures is given in section below. Shells for unique tables and listings are provided in a separate Mock-Up Tables, Figures and Listings document.