Title: An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-931, a Cell Division Cycle 7 (CDC7) Inhibitor, in Adult Patients With Advanced Nonhematologic Tumors

NCT Number: NCT02699749

Statistical analysis plan Approve Date: 15-MAR-2020

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN

TAK-931

An Open-Label, Phase 1, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-931, a Cell Division Cycle 7 (CDC7) Inhibitor, in Adult Patients with Advanced Nonhematologic Tumors

Protocol #: 1002

Protocol Amendment 4

SAP Version:	Date of Statistical Analysis Plan:
Final	15 MAR 2020

PPD

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1. LIST OF ABBREVATION

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve from the time 0 to 12 hours
AUC_{24}	area under the plasma concentration-time curve from the time 0 to 24 hours
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
BID	twice daily
BLRM	Bayesian Logistic Regression Modeling
BNP	B-type natriuretic peptide
CDC7	cell division cycle 7
CL/F	apparent oral clearance
CLr	renal clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CSR	clinical study report
CCI	CCI
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
MCM2	minichromosome maintenance complex-2
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
PD	progressive disease (disease progression)
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
QD	once daily
$R_{ac(AUC)}$	accumulation ratio based on AUC
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose(s)
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
TK	toxicokinetic
t_{max}	time to first occurrence of maximum (peak) concentration
WHO	World Health Organization
pMCM2	phosphorylation of minichromosome maintenance complex-2

2. INTRODUCTION

The purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry.

2.1 Study Design

This is a phase 1, open-label, dose-escalation study designed to evaluate the safety, tolerability, and PK and to determine the MTD or a maximum tested dose of TAK-931, a CDC7 inhibitor, in adult patients with histologically confirmed, nonhematologic (solid) tumors. Dose escalation of TAK-931 will be cohort based with an adaptive design using Bayesian Logistic Regression Modeling (BLRM) with PK guidance.

Approximately 100 patients will be enrolled into this study in up to 8 to 9 dose cohorts. A minimum of 3 patients will be enrolled in each cohort to support safety and PK guidance. Once the MTD is defined, a safety expansion cohort of 15 patients will be initiated including patients treated at the MTD.

TAK-931 initially will be administered for 14 days of each 21-day treatment cycle. TAK-931 will be given as a single daily dose (QD). The starting dose will be 30 mg. If the PK from the first 2 dose escalation cohorts supports BID dosing, then study drug administration in subsequent cohorts may transition to a BID dosing schedule either before or when a geometric mean C_{max} of 400 ng/mL is predicted after a single dose of TAK-931 on C1D1 in a cohort.

Study drug may be discontinued early if a patient experiences study drug-related toxicities, if a patient requires prolonged treatment interruption to recover from a toxicity, or if the toxicity recurs upon retreatment. Patients will attend the End-of-Study visit 30 to 40 days after receiving their last dose of study drug or before initiating new anti-cancer therapy (whichever comes first).

To ensure patient safety and to minimize the number of patients exposed to non-efficacious doses, the dose escalation will consist of an initial accelerated escalation phase in which dose

levels are increased by 100%. The accelerated escalation phase will transition to modified Fibonacci escalation steps after 1 patient experiences a DLT in Cycle 1 or when 2 patients experience ≥Grade 2 hematologic or non-hematologic related or possibly related drug toxicity or when geometric mean plasma C_{max} for the cohort reaches or exceeds 400 ng/mL. The dose escalation steps will be modified, as needed, based on clinical safety and PK results. The escalation steps may also be modified based on accumulating PK data and BLRM that would provide narrower escalation steps and potentially decrease the number of patients exposed to doses above the MTD. In addition, there will be a minimum of 1 week interval between C1D1 of the first patient dosed and C1D1 of the second patient dosed for each dose escalation cohort. Subsequent patient dosing (third patient per cohort and beyond) may occur at a shorter interval (eg, <7 days from previous patient's C1D1 dosing) but no more than 1 patient will undergo C1D1 dosing within a 1-day period. At the MTD dose level, an expansion cohort of 15 patients (including patients treated at the MTD) will be treated to better define the safety and tolerability of TAK-931.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objectives are:

- To evaluate the safety and tolerability of TAK-931.
- To identify the MTD or maximum tested dose of TAK-931 in adult patients with nonhematologic tumors.

2.2.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of TAK-931 in adult patients with nonhematologic tumors.
- To assess the pharmacodynamic effect of TAK-931 by measuring basal and postdose levels of phosphorylated MCM2 (Ser40), a CDC7 substrate, in skin.
- To assess preliminary clinical activity of TAK-931 as measured by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1).

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3. POPULATIONS FOR ANALYSIS

3.1 Safety population

The safety population is defined as all patients who receive any amount of study drug. All safety analyses will be based on the safety population.

3.2 Pharmacokinetic population

The pharmacokinetic population is defined as all patients for whom there are sufficient dosing and TAK-931 concentration-time data to reliably estimate the PK parameter(s). PK analyses will be performed using the PK population.

3.3 Pharmacodynamics population

The pharmacodynamics population is defined as all patients who receive at least the first dose of TAK-931, have a baseline skin punch CCI biopsy sample, and have at least 1 additional skin punch CCI biopsy taken during Cycle 1 of treatment. The skin CCI biopsies must contain detectable basal pMCM2 signals to permit an estimate of pMCM2 (Ser40) levels. Pharmacodynamic analyses will be performed using the pharmacodynamics population.

3.4 Response-Evaluable Population

The response-evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at baseline, and at least 1 post-baseline response assessment. The response-evaluable population will be used for the analysis of ORR and DOR.

3.5 DLT-Evaluable Population

The DLT-evaluable population is defined as all patients who receive at least 75% of their planned TAK-931 doses (ie, 11 QD doses or 21 BID doses) for their first cycle of treatment (unless interrupted by related AEs) and who have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Patients who receive <75% of doses of TAK-931 (ie, 11 QD doses or 21 BID doses) in Cycle 1 for reasons other than related AEs are not evaluable for DLT and will be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level. The DLT-Evaluable population will be used for analysis of DLT.

4. HYPOTHESES AND DECISION RULES

Statistical analyses will be descriptive and graphical in nature and no formal hypothesis testing will be performed.

5. INTERIM ANALYSIS

As this is a phase 1 study there is no formal interim analysis. There will be an ongoing review of safety data with the medical monitor and study investigators.

6. STATISTICAL METHODOLOGY

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed. Summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (calculated using non-missing values) per category for categorical data, unless specified otherwise.

Subjects will be analyzed at the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

6.1 Sample Size Justification

It is anticipated that approximately 36 to 40 patients will be enrolled in up to 8 to 9 dose escalation cohorts. Once the MTD is determined, a safety expansion cohort of 15 patients (including patients treated at the MTD) will be initiated.

An adaptive approach with BLRM will be used for dose escalation. BLRM implements dose escalation with overdose control principle [1,2] that informs dose escalation decisions and MTD estimation, along with clinical safety data evaluation and PK guidance (ie, the projected geometric mean C_{max} for the subsequent cohort does not exceed 800 ng/mL to allow dose escalation).

The 2-parameter model used is as follows:

$$\ln\left(\frac{\pi_i}{1-\pi_i}\right) = \ln(\alpha) + \beta \ln\left(\frac{\text{dose}_i}{\text{dose}_{ref}}\right), \quad \alpha > 0, \beta > 0$$

where π_i is the DLT rate for dose i and dose_{ref} is a reference dose. A quantile-based, non-informative, bivariate normal prior will be used for ln(α) and ln(β). This prior will be assigned based on pre-study estimates of the DLT rate at each dose level, as described in Neuenschwander, et al. [1].

The model will be updated after each group of 3 patients enrolled in the current dose level. For each dose level, the posterior probability of having DLT rates that fall into the following intervals will be estimated:

[0, 0.16): underdosing.
[0.16, 0.33): target toxicity.
[0.33, 1.00]: excessive toxicity.

The next recommended dose will be selected as described in Section **Error! Reference s ource not found.** of protocol.

The accuracy of the BLRM recommendation relies on the true DLT rate, thus the clinical PK guidance and safety evaluation are combined to support the dose escalation.

6.2 Randomization and Stratification

No randomization or stratification will be performed in this study. During dose escalation, subjects will be enrolled in successive dose cohorts.

6.3 Unblinding

Not applicable.

6.4 Data Handling

6.4.1 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

6.4.1.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits, with the exception of prior therapies (Section 6.4.1.2)

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first treatment. Otherwise, the 15th will be used.
- If only a year is present, and it is the same as the year of the first treatment, the 15th of January will be used unless it is later than the first treatment, in which case the date of the first of January will be used.
- If only a year is present, and it is not the same as the year of the first treatment, the 15th of June will be used, unless other data indicates that the date is earlier, in which case the 15th of January will be used. .

6.4.1.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data. If the resolution date of a resolved adverse event (AE) or the stop date of a concomitant therapy is missing, the following rules are to be used unless conflicting data exists: if month and year are present and the day of the month is missing, the last day of the month is imputed. If only a year is present, the 31st of December is used. After imputation, the imputed dates will be compared against the date of death, if available. If the date is later than the date of death, the date of death will be used as the imputed date instead.

In cases where the onset date of an adverse event is completely or partially missing, the following imputation rules will be used:

1. When month and year are present and the day of the month is missing,
    - If the onset month and year are the same as the month and year of first treatment with study drug, the day of first treatment or the day-component of the resolution date are imputed, whichever is earliest.
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.
2. When only a year is present, or no components of the onset date are present,
    - If the resolution date is available, the earlier of the resolution date (possibly imputed) and the date of first treatment will be used.
    - If the resolution date is missing, and the onset-year is the same as the year of first treatment with study drug, then the date of first treatment with study drug is used.
    - Otherwise if only a year is present, the 1st of January of that year is imputed.
3. If none of the previous rules can be applied, then the date of first treatment with study drug is imputed as the onset date.

The imputation rules for missing/partial start dates of concomitant therapies will be the same as the above with the exception as follows:

For prior therapy data, no imputation will be done for start dates.

The imputation rules for missing/partial start dates of subsequent therapies recorded as concomitant medications will be the same as the above with exceptions as follows.

1. When month and year are present and the day of the month is missing,

    a. If the month and year of the start date are the same as the month and year of treatment termination, the day of treatment termination or the day-component of the stop date is imputed, whichever is earliest.
    b. If the start month and year are not the same as the month and year of treatment termination, the first day of the month is imputed.
2. When only a year is present, or no components of the start date are present, the date will not be imputed.

6.4.2 **Definition of Baseline Values**

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. For the ECG summaries, the baseline is defined as the average of the triple 12-lead ECG measurements at the time closest to, but prior to, the start of TAK-931 administration.

6.4.3 **Windowing of Visits**

All data will be categorized based on the scheduled visit at which they were collected. These visit designators are pre-defined values that appear as part of the visit tab in the eCRF.

6.4.4 **Justification of Pooling**

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

6.5 **Patient Disposition**

A disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study population, primary reason to discontinue from the treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be presented by dose level and be based on the number of patients in the safety population.

A listing will present data concerning patient disposition.

6.6 Demographics and Baseline Disease Characteristics

6.6.1 Demographics

Demographics and baseline characteristics will be summarized by treatment dose group in a descriptive fashion for the ITT population. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters as appropriate.

Demographic data will also be presented in a by-patient listing.

6.6.2 Medical History

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the status (whether it is resolved or ongoing).

6.6.3 Baseline Disease Status

Baseline disease characteristics will be summarized by the number and percentage of patients by dose escalation patients and total. Time since initial diagnosis (months) will be included in the summary as well as the stage of the disease. Eastern Cooperative Oncology Group (ECOG) performance status will be summarized similarly in the same table.

Separate by-patient listing will be presented for baseline disease and ECOG performance status.

6.6.4 Concomitant Medications

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary for patients in the safety population. The number and percentage of subjects taking concomitant medications will be tabulated by WHO drug generic term, from the first dose of study treatment through 30 days after the last dose of study medication or until the start of subsequent antineoplastic therapy, whichever occurs first

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

6.6.5 Study Treatments

TAK-931 initially will be administered for 14 days of each 21-day treatment cycle. TAK-931 will be given as a single daily dose (QD). The starting dose will be 30 mg. If the PK

from the first 2 dose escalation cohorts supports BID dosing, then study drug administration in subsequent cohorts may transition to a BID dosing schedule either before or when a geometric mean Cmax of 400 ng/mL is predicted after a single dose of TAK-931 on C1D1 in a cohort.

6.6.5.1 **Extent of Exposure**

Extent of exposure to TAK-931 will be characterized by total amount of dose taken in mg, total number of dose taken, number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, and ≥12 treated cycles, and relative dose intensity (%). Duration of treatment (days), and number and percentages of patients who had >=3, >=6, … weeks of treatment will be summarized for patients in the safety population.

A treated cycle is defined as a cycle in which the patient received any amount of any treatment drug. Relative dose intensity (%) is defined as 100 x (total dose received in mg) / (sum of prescribed dose over all treated cycles). Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study.

Dosing data will also be presented in a by-patient listing.

6.6.5.2 **Treatment Modifications**

The actions on TAK-931 (reduce prescribed, reduce non-prescribed, increased prescribed, increased non-prescribed, held, missed, interrupted, delayed, discontinued permanently) will be summarized over all treatment periods, and by each of Cycle. Reasons for dose modification may also be tabulated similarly.

6.6.6 **Efficacy Analysis**

The secondary efficacy parameters include ORR (CR + PR), PFS, and DOR.

The ORR is defined as the proportion of patients who achieved PR or CR. The estimate of the ORR will be presented with 2-sided 95% exact binomial confidence intervals for each dose cohort. ORR will be analyzed using the response-evaluable population.

Progression-free survival is defined as the time from the date of first dose to the date of first documentation of progressive disease or death due to any cause, whichever occurs first. The Kaplan-Meier survival curves, 25th, 50th (median), and 75th percentiles (if estimable), along with their 2-sided 95% confidence intervals will be provided for each dose cohort. PFS will be analyzed using safety population.

The DOR is defined as the time from the date of first documentation of a response (PR or better) to the date of first documentation of progressive disease. Patients without documentation of progressive disease at the time of analysis will be censored at the date of their last response assessment that is stable disease or better. The DOR will be analyzed using the Kaplan-Meier method. The DOR will be analyzed based on the responders in the response-evaluable population.

6.6.7 **Pharmacokinetic Analyses**

PK parameters will be estimated using non-compartmental methods with WinNonlin® Professional Version 6.1 or higher (Pharsight Corp., Mountain View, CA). The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Concentration data that are identified as anomalous may be excluded from the concentration summaries and plots and will not be used in the calculation of PK parameters. Evidence or explanations will be provided to justify the exclusion of data.

The plasma and urine PK of TAK-931 after the first dose on C1D1 and after multiple doses on C1D8 will be determined based on the PK parameters below, as permitted by data.

- Area under the plasma concentration-time curve from time 0 to time of last measurable concentration ($AUC_{0\text{-last}}$)
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-inf}}$)
- Area under the plasma concentration-time curve from time 0 to 24 hr (AUC_{24})
- Area under the plasma concentration-time curve from time 0 to 12 hr (AUC_{12} for BID dosing on C1D1 and after administration of multiple doses on C1D8))
- Observed maximum plasma concentration (Cmax)
- Time to observed maximum plasma concentration (Tmax)
- Terminal disposition phase rate constant (λ_z)
- Terminal phase half-life (t1/2)
- Apparent oral clearance (CL/F)

- Apparent terminal phase volume of distribution (Vz/F)

Individual TAK-931 concentration versus time data and individual PK parameters will be presented in listings and also tabulated using summary statistics by dose group. Individual and mean plasma concentration-time profiles will be plotted by dose group.

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of deviation, geometric mean, median, minimum value, and maximum value) will be used to summarize the calculated PK parameters. For T_{max}, only median, minimum value, and maximum value will be calculated only if quantifiable and/or reportable values are available for at least 50% of the observations. A minimum of 2 patients are required to show the mean and geometric mean, and at least 3 patients are required to show the standard deviation and CV. The number of observations above the limit of quantification will be shown for plasma concentration-time data.

The overall summary statistics will be calculated across dose groups for PK parameters will be provided that there is no readily apparent nonlinear pharmacokinetics across dosing groups.

TAK-931 plasma concentration-time data will be listed using the PK-Evaluable population.

6.6.8 **Pharmacodynamic Analysis**

The change from baseline of pMCM2 (Ser40) levels in skin on C1D8 will be descriptively summarized by dose cohort. The change from baseline of pMCM2 (Ser40) levels may also be descriptively summarized in skin CCI biopsies on C1D15 at the MTD or maximum tested dose.

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6.6.10 **Safety Analyses**

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes, or abnormalities in the subject's physical examination, vital signs, ECG, and clinical laboratory results.

These analyses will be performed using the safety population.

6.6.10.1 Dose Limiting Toxicities (DLTs)

A by-subject listing of DLTs which occur during Cycle 1 of treatment will be presented by schedule and dose level for all subjects enrolled during the dose escalation portion of this study. Subjects will be grouped by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

6.6.10.2 Adverse Events

AEs will be coded using the MedDRA dictionary, version 18.0. All AEs will be presented in a by-patient listing. Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and up through 30 days after the last dose of study medication or until the start of subsequent antineoplastic therapy, whichever occurs first, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator. Treatment-emergent AEs will be tabulated according to the MedDRA by system organ class, high level terms and preferred terms and will include the categories listed below. Patients with the same AE more than once will have that event counted only once within each body system, once within each high level term, and once within each preferred term.

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients in the safety population) will be tabulated by system organ class and preferred term. Patients with the same AE more than once will have that event counted only once within each system organ class and once within each preferred term.

6.6.10.3 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAE will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment emergent AE status).

6.6.10.4 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 30 days of the last dose of study drug.

6.6.10.5 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented.

6.6.11 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a laboratory value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

Laboratory test results from the central laboratory will be used when they are available. Laboratory test results from local laboratory will only be used when no central laboratory test results exist at the same scheduled sample collection time point.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used. In case more than one assessment is available on the same date, the later assessment will be used.

Laboratory test results will be summarized descriptively according to the scheduled sample collection time points. Actual values and change from baseline will be summarized over time. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE for toxicity from baseline to post baseline worst CTCAE grade. Parameters to be tabulated will include:

- Hematology: hemoglobin, hematocrit, platelets, absolute neutrophil counts (ANC), lymphocytes, eosinophils, and WBC
- Clinical chemistry: ALT/SGPT, AST/SGOT, alkaline phosphatase, bilirubin (total), calcium, creatinine, glucose, hemoglobin A1c, magnesium, phosphate, potassium, and sodium

Box plots over time for liver function tests will be produced.

E-dish plots for ALT/bilirubin and AST/bilirubin will also be produced.

By-patient listings to be presented include hematology, clinical chemistry and urinalysis.

Urinalysis parameters include turbidity and Color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, urobilinogen, glucose, leukocytes.

Change from baseline in below parameters will be provided

- Metabolic panel – Cholesterol, Triglycerides, high density lipoprotein (HDL) cholesterol, low density protein (LDL) cholesterol, and hemoglobin A1c
- Fasting serum glucose

By-patient listings to be presented include cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density protein (LDL) cholesterol, fasting plasma glucose and hemoglobin A1c.

The incidence of all Cycle 1 ≥Grade 2 hepatic toxicities with a duration >72 hours and ≥Grade 3 hematologic toxicities with a duration >72 hours will also be tabulated for each dose cohort.

6.6.12 Electrocardiograms

Electrocardiogram actual results including abnormalities will be listed in a by-patient listing.

6.6.13 Vital Signs

The actual values and changes from baseline of vital sign parameters including oral temperature, heart rate, systolic and diastolic blood pressure, and weight, will be

summarized over time for both Phase 1b and Phase 2 analyses, and will also be presented in a by-patient listing.

7. PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all analyses.

7.2 Rules and Definitions

Subject populations are defined in Section 3.

Baseline values are defined in Section **Error! Reference source not found.**.

8. REFERENCES:

1. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008;27(13):2420-39.