Title: Phase 1 Study to Evaluate the Effect of MLN0128 on the QTc Interval in Patients With Advanced Solid Tumors

NCT Number: NCT02197572

SAP Approve Date: February 18, 2015

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# STATISTICAL ANALYSIS PLAN

***A Phase 1 Study to Evaluate the Effect of MLN0128 on the QTc Interval in Patients With Advanced Solid Tumors***

Protocol #: C31002

| SAP Version: | Date of Statistical Analysis Plan: |
|---|---|
| Final | 18 Feb 2015 |

## Approval Signatures

PPD

Feb. 24, 2015
Date

23 Feb 2015
Date

23 Feb 2015
Date

25 Feb 2015
Date

25 Feb 2015
Date

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## List of Abbreviations and Definitions of Terms

| Abbreviation | Term |
|---|---|
| AE(s) | adverse event (or events) |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATCC | Anatomical Therapeutic Chemical Classification |
| ATP | adenosine triphosphate |
| $AUC_{inf}$ | area under the plasma concentration versus time curve from zero to infinity |
| $AUC_t$ | area under the plasma concentration versus time curve from zero to the last measurable concentration |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CI | confidence interval |
| $C_{max}$ | maximum (peak) plasma concentration |
| $CO_2$ | carbon dioxide |
| CRF | case report form |
| DLT | dose limiting toxicity |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| FDA | Food and Drug Administration |
| GGT | gamma glutamyl transferase |
| ICF | informed consent form |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| PK | pharmacokinetic |
| QT | measure of the time between the start of the Q wave and the end of the T wave in the electrical cycle of the heart; electrical depolarization and repolarization of the left and right ventricles of the heart |
| $QT_c$ | rate-corrected QT interval (millisec) |
| $QT_cB$ | rate-corrected QT interval (millisec) with Bazett correction |
| $QT_cF$ | rate-corrected QT interval (millisec) Fridericia correction |
| $QT_cI$ | individual baseline corrected rate-corrected QT interval (millisec) |
| QW | every week; once weekly |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| $t_{1/2}$ | terminal disposition half-life |

| Abbreviation | Term |
|---|---|
| TEAE | treatment emergent adverse event |
| $T_{max}$ | first time to maximum plasma concentration |
| ULN | upper limit of the normal range |
| US | United States |
| WHO | World Health Organization |

# 1. INTRODUCTION

In general, 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 addresses 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.

This SAP only covers the analyses to be performed for the clinical data collected at the sites in the eCRF. The ECG QTc analyses from the Holter monitor will be in a separate SAP prepared by CardioCore. The QTc-PK analyses will be in a SAP prepared by Metrum Research Group.

## 1.1 Study Design

This is an open label, single-arm, multicenter study to evaluate the effect of a single dose of 40 mg MLN0128 on the electrocardiographic QT/$QT_c$ interval in patients with advanced solid tumors. The study will collect time-matched PK and ECG data before and after MLN0128 administration at the time points specified in the Schedule of Events in the protocol.

Patients may continue to receive MLN0128 if, in the opinion of the investigator, the patients are deriving clinical benefit. Treatment may continue until disease progression, unacceptable MLN0128-related toxicity, withdrawal of consent, or for up to 12 months (whichever occurs first).

Approximately, 30 patients will be enrolled from approximately 6 study centers in the US.

## 1.2 Study Objectives

Primary objective:

- To characterize the effect of a single dose of 40 mg MLN0128 on the electrocardiographic QT/$QT_c$ interval in patients with advanced solid tumors.

Secondary objective:

- To evaluate the safety, tolerability, and pharmacokinetics of MLN0128 in patients with advanced solid tumors.

## 2. POPULATIONS FOR ANALYSIS

### 2.1 Safety Population

All patients who receive at least 1 dose of MLN0128 will be included in the safety population. This population will be used for safety analyses.

### 2.2 PK Population

All patients who receive at least 1 dose of MLN0128 and have sufficient concentration-time data to calculate one or more PK parameters will be included in the PK population. All PK analyses will be performed using the PK population.

## 3. HYPOTHESES AND DECISION RULES

Not applicable.

## 4. INTERIM ANALYSIS

Not applicable.

## 5. STATISTICAL METHODOLOGY

Statistical analyses will be primarily descriptive and graphical in nature.

In general, the number of observations, mean, standard deviation (SD), median, minimum, and maximum will be displayed for continuous variables, and the number and percent for categorical data, unless specified otherwise. For PK related parameters, the geometric mean and coefficient of variation will also be presented.

## 5.1 Sample Size Justification

Based on historical data, the within-subject standard deviation in $QT_cF$ change from baseline is approximately 9 msec. A sample size of 30 evaluable patients will be needed to detect a half-width of 2.7 msec of a 2-sided 90% CI for the mean change from baseline in $QT_cF$.

## 5.2 Randomization and Stratification

Not applicable.

## 5.3 Unblinding

Not applicable.

## 5.4 Data Handling

### 5.4.1 Methods for Handling Missing Data

All available 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.

#### 5.4.1.1 Missing/Partial Dates in Adverse Events/Concomitant Therapies

Missing and incomplete start dates will be imputed based on the algorithm described below.

The algorithm will be used only if the end date indicates that the adverse event was not resolved or the therapy was not ended before the first administration of study drug.

Adverse events or concomitant therapies with start dates that are completely or partially missing will be analyzed as follows:

If the start date has month and year but day is missing, the adverse event will be considered treatment-emergent or the therapy concomitant if both the month and year of the start date are on or after the month and year of the date of the first dose of MLN0128 and on or before the month and year of the date of the last dose of MLN0128 plus 30 days.

If the start date has year, but day and month are missing, the adverse event will be considered treatment -emergent or the therapy concomitant if the year of the start date is on or after the year of the date of the first dose of MLN0128 and on or before the year of the date of the last dose of MLN0128 plus 30 days.

If the start date of an adverse event or therapy is completely missing, then the event is assumed to be treatment-emergent or the therapy concomitant.

### 5.4.2 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.

### 5.4.3 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

### 5.4.4 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.

### 5.4.5 Withdrawals, Dropouts, Lost to Follow-up

Patients who are withdrawn from treatment before completing study-required PK/ECG assessments for reasons other than DLTs will be replaced.

## 5.5 Patient Disposition

Patient disposition will be summarized as the number and percentage of patients in the safety and PK populations, and the reason study drug was discontinued. All percentages will be based on the number of patients enrolled.

## 5.6 Demographics and Baseline Disease Characteristics

### 5.6.1 Demographics

Demographic and baseline characteristics will be summarized. These include age, gender, ethnicity, race, height, weight and body mass index (BMI).

BMI = weight / height$^2$, where weight is in kilograms and height in meters.

### 5.6.2 Medical History

#### 5.6.2.1 General Medical History

Medical history will be presented in by-patient listings.

#### 5.6.2.2 Disease-Specific History

The following disease-specific characteristics will be summarized: tumor type, stage, Eastern Cooperative Oncology Group (ECOG) performance status and site of cancer involvement. Percents are based on the number of patients in the safety population.

ECHO data collected at Baseline and Prior Therapies will be presented in by-patient listings.

## 5.7 Treatments and Medications

### 5.7.1 Concomitant Medications

Concomitant medications will be coded using the March 2014 version of the World Health Organization (WHO) Drug Dictionary Enhanced. The number and percentage of patients taking concomitant medications from the date of the first dose of study drug will be tabulated by generic term.

### 5.7.2 Study Treatments

Patients will be required to swallow 8, 5-mg capsules for a total dose of 40 mg MLN0128 on Cycle 1, Day 1. To mitigate nausea and vomiting, patients will be administered an antiemetic agent on Cycle 1, Day 1 as an intravenous infusion (IV) over 30 seconds, at least 30 minutes before study drug administration. After completing the required PK/ECG assessments at Cycle 1, Day 3, patients may continue treatment with MLN0128. For patients continuing treatment with MLN0128, the drug is administered at a dose of 30 mg once weekly (QW) in continuous cycles of 28 days.

#### 5.7.2.1 Extent of Exposure

The total amount of dose taken in mg, number of treated cycles and the relative dose intensity will be summarized in each cycle and overall. A treated cycle is defined as a cycle in which the patient received any amount of study drug. The numbers and percentages of patients who had 1, 2, 3 …..etc. treated cycles will also be presented.

Relative dose intensity (%) for MLN0128 is defined as 100x(total amount of dose taken ((mg))/(prescribed dose per day*total number of treated days in cycle*number of treated cycles).

#### 5.7.2.2 Treatment Compliance and Modifications

Action on study drug will be summarized across the cycles

## 5.8 Efficacy Analyses

The investigator's assessment of response including tumor lesion measurement (targeted and non-targeted), new lesions, will be provided in a data listing.

## 5.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

### 5.9.1 Pharmacokinetic Analyses

The PK population will be used for the description of the concentration-time profiles and for the estimation of the PK parameters.

Descriptive statistics (number of patients, mean, SD, geometric mean, median, minimum, maximum, and coefficient of variation) will be presented for the plasma PK parameters listed below. Individual and mean plasma concentration data will be plotted over time.

Data permitting, summary statistics for the following PK parameters will be provided:

- Area under the plasma concentration-time curve from time 0 to time of last measurable concentration($AUC_{last}$)
- Area under the plasma concentration-time curve from time 0 to infinity ($AUC_{inf}$)
- Area under the plasma concentration-time curve from time 0 to 48 hr ($AUC_{48hr}$)
- Observed maximum plasma concentration ($C_{max}$)
- Time to observed maximum plasma concentration ($T_{max}$)
- Terminal disposition phase rate constant ($lambda_z$)
- Terminal phase phase half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Apparent terminal phase volume of distribution (Vz/F)

QTc-PK analyses will be performed by Metrum Research Group. The details are presented in a SAP prepared by Metrum Research Group.

### 5.9.2 Pharmacodynamic Analyses

Not applicable.

### 5.9.3 Biomarker Analysis

Not applicable.

## 5.10 Safety Analyses

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

These analyses will be performed using the safety population.

### 5.10.1 Adverse Events

#### 5.10.1.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities ( MedDRA), version 17.0 or higher.

A treatment-emergent AE (TEAE) is an AE that occurs on or after the date of the first dose of study drug and up through 30 days after the last dose of study drug.

The number and percentage of patients experiencing at least 1 TEAE will be tabulated by MedDRA primary system organ class, high-level term and preferred term. For the number of patients with AEs, patients reporting the same event 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.

Tabular summaries of the following TEAEs will also be provided:

- TEAEs related to Study Drug
- Grade 3 or greater TEAEs
- Grade 3 or greater TEAEs related to Study Drug
- Most common (>= 10% of patients) TEAEs by maximum severity grade

The following adverse events of interest will be tabulated:

| Adverse event of interest | MedDRA Preferred Term |
|---|---|
| Hyperglycemia | Glucose tolerance impaired, Hyperglycaemia, Impaired fasting glucose |
| Rash | Fixed eruption, Mucocutaneous rash, Rash, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash rubelliform, Rash scarlatiniform, Rash vesicular, Dermatitis exfoliative, Drug eruption, Drug hypersensitivity, Drug rash with eosinophilia and systemic symptoms, Reaction to drug excipients, Toxic skin eruption, Administration related reaction, Erythema, Generalised erythema, Rash erythematous, Rash popular, Rash papulosquamous |
| Renal Insufficiency (MedDRA Standardized Medical Query) | Acute phosphate nephropathy , Acute prerenal failure (Narrow), Anuria (Narrow), Azotaemia (Narrow), Continuous haemodiafiltration (Narrow), Dialysis (Narrow), Haemodialysis (Narrow), Neonatal anuria (Narrow), Nephropathy toxic (Narrow), Oliguria (Narrow), Peritoneal dialysis (Narrow), Prerenal failure (Narrow), Renal failure (Narrow), Renal failure acute (Narrow), Renal failure neonatal (Narrow), Renal impairment (Narrow), Renal impairment neonatal (Narrow), Albuminuria (Broad), Blood creatinine abnormal (Broad), Blood creatinine increased (Broad), Blood urea abnormal (Broad), Blood urea increased (Broad), Blood urea nitrogen/creatinine ratio, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Creatinine urine abnormal (Broad), Creatinine urine decreased (Broad), Crystal nephropathy (Broad), Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Hypercreatininaemia (Broad), Nephritic syndrome (Broad), Nephritis (Broad), Oedema due to renal disease (Broad), Protein urine present (Broad), Proteinuria (Broad), Renal function test abnormal (Broad), Renal transplant (Broad), Renal tubular disorder (Broad), Renal tubular necrosis (Broad), Tubulointerstitial nephritis (Broad), Urea renal clearance decreased (Broad), Urine output decreased (Broad) |

| | |
|---|---|
| Mucosal Inflammation | Burning sensation mucosal, Mucosal erosion, Mucosal excoriation, Mucosal exfoliation, Mucosal hyperaemia, Mucosal inflammation, Mucosal necrosis, Mucosal ulceration, Aphthous stomatitis, Mouth ulceration, Oral mucosa erosion, Stomatitis, Stomatitis haemorrhagic, Stomatitis necrotizing, Oral discomfort, Oral mucosal blistering, Oral mucosal erythema, Oral mucosal exfoliation, Oropharyngeal blistering, Oropharyngeal discomfort, Oropharyngeal pain |
| Asthenic Conditions | Asthenia, Fatigue, Lethargy, Listless, Malaise, Sluggishness, Muscle Weakness |

Events will be considered related to study drug if the investigator answered "yes" to the following question: "Is there a reasonable possibility that the adverse event was associated with the study medication?"

Intensity is determined using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 4.03.

By-patient listings will be produced for all DLTs.

All TEAEs will be presented in by-patient listings.

#### 5.10.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment emergent serious AE (SAE) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. Drug-related SAEs 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 status).

#### 5.10.1.3 Deaths

A by-patient listing of the deaths will be presented. All deaths occurring on-study will be displayed (regardless of treatment emergent status). On-study death is defined as death that occurs during the period from the first dose of study drug through 30 days after the last dose of study drug.

#### 5.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of TEAEs resulting in discontinuation of study drug will be presented.

### 5.10.2 Laboratory Data

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.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be presented according to the scheduled sample collection time points. Unscheduled laboratory test results will be included in the by-patient listings and in shift tables.

Descriptive statistics for the actual values of the clinical laboratory parameters and/or change from baseline will be presented for all scheduled time points. Mean laboratory values over time (up to Cycle 6) will be plotted for hemoglobin, platelets, leucocytes, neutrophils, lymphocytes, creatinine, glucose, Alanine aminotransferase (ALT), urate, Aspartate aminotransferase (AST), phosphate, blood urea nitrogen (BUN), sodium, potassium, chloride, calcium, magnesium, glycosylated hemoglobin, total cholesterol, triglycerides, high density lipoprotein cholesterol, and low density lipoprotein cholesterol. Other graphical displays such as scatter plots of baseline versus worst post-baseline values will be presented.

Shift tables based on changes in NCI CTC AE grade from baseline to worst post-baseline value will be presented.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, platelets, leucocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- Clinical chemistries: bilirubin, creatinine, alkaline phosphatase (ALP), glucose, ALT, urate, AST, phosphate, gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), albumin, BUN, sodium, potassium, carbon dioxide ($CO_2$), chloride, calcium, magnesium and glycosylated hemoglobin.
- Urinalysis: turbidity, color, pH, nitrite, protein, leukocytes, glucose, ketones, bilirubin, occult blood, specific gravity and urobilinogen.

- Fasting Lipid Profile: total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol.

### 5.10.3 Electrocardiograms

The primary analysis of ECG parameters is from the continuous Holter Monitor recordings. The ECG QTc analyses from the Holter monitor will be in a separate SAP prepared by CardioCore.

All ECG parameters and the overall interpretation from the single 12-lead ECG will be listed by patient.

### 5.10.4 Vital Signs

Vital sign results (diastolic and systolic blood pressure, temperature, heart rate) and body weight will be summarized descriptively by scheduled time point as follows:

- Baseline value
- Minimum post-baseline value
- Maximum post-baseline value

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

By-patient listings will be produced.

## 6. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

Not applicable.

# 7. PROGRAMMING CONSIDERATIONS

## 7.1 Statistical Software

SAS version 9.2 (or higher) will be used for all safety and efficacy analyses. PK parameters will be estimated using non-compartmental analysis (NCA) with Phoenix WinNonlin Version 6.2 or newer.

## 7.2 Rules and Definitions

Patient populations are defined in Section 2.

Baseline values are defined in Section 5.4.2.

Treatment-emergent AEs are defined in Section 5.10.1.1.

# 8. REFERENCES

Not applicable.