![Takeda logo]

Title: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

NCT Number: NCT02412722

SAP Approve Date: 12Aug2015

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 (PPD) information or company confidential information (CCI).

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

- Named persons or organizations associated with the study.

- 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.

STATISTICAL ANALYSIS PLAN

A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MLN0128 (an Oral mTORC 1/2 Inhibitor) as a Single Agent and in Combination With Paclitaxel in Adult Patients With Advanced Nonhematologic Malignancies

Protocol #: MLN0128-1004

SAP Version:
Final

Date of Statistical Analysis Plan:
12Aug2015

Approval Signatures

PPD

13 Aug 2015
_____
Date

13 Aug 2015
_____
Date

12 Aug 2015
_____
Date

12th Aug 2015
_____
Date

TABLE OF CONTENTS

TABLE OF CONTENTS

List of Abbreviations and Definitions of Terms

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
API	active pharmaceutical ingredient
BMI	body mass index
AUC	area under the plasma concentration versus time curve
BUN	blood urea nitrogen
CI	confidence interval
Cmax	maximum plasma concentration
CRF	case report form
CSR	clinical study report
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HbA1c	glycosylated hemoglobin
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic(s)
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SLD	Sum of the longest diameter
TEAE	treatment emergent adverse event
Tmax	first time of occurrence of maximum (peak) concentration
SD	standard deviation
WBC	white blood cell
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.

1.1   **Study Design**

This study is a multicenter, open-label, phase 1 trial of MLN0128 administered orally both as a single agent and in combination with IV infusions of paclitaxel in adult patients with advanced nonhematologic malignances for whom standard, curative, or life-prolonging anticancer treatment does not exist or is no longer effective. The study will consist of 3 arms: a Single-Agent QD Arm, a Combination Arm, and a Single-Agent QW Arm. The 3 arms will enroll in parallel and will administer study treatment in repeated 28-day cycles.

Study eligibility will be determined during the Screening period, which may last for up to 28 days before the first dose of study drug is administered. Patients who meet all eligibility criteria and provide written informed consent will be enrolled.

The Single-Agent QD Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach and will additionally characterize the PK profile when taken with a standardized high-fat breakfast. In the same patients, the PK of MLN0128 unmilled API capsules when taken on an empty stomach will also be assessed as a point of reference for comparison of milled API capsule PK. The PK assessments will be performed during a PK Run-In period during which each patient will receive a total of three 4-mg doses of MLN0128 as described below:

- PK Run-In Visit 1: MLN0128 4-mg unmilled API capsule taken on an empty stomach.
- PK Run-In Visit 2 (24 hours [$\pm$ 1 hr] after PK Visit 1): 24-hour postdose PK sample collected.
- PK Run-In Visit 3 ($\geq$ 48 hours after PK Visit 1): MLN0128 4-mg milled API capsule taken with a standardized high-fat breakfast.

- PK Run-In Visit 4 (24 hours [± 1 hr] after PK Visit 3): 24-hour postdose PK sample collected.

- PK Run-In Visit 5 (≥ 48 hours after PK Visit 3): MLN0128 4-mg milled API capsule taken on an empty stomach.

- PK Run-In Visit 6 (24 hours [± 1 hr] after PK Visit 5): 24-hour postdose PK sample collected. Note: If scheduling permits, Visit 6 can be combined with Cycle 1 Day 1 of the Study Treatment period.

Each patient in the Single-Agent QD Arm will complete the PK Run-In period within 14 days before Cycle 1 Day 1 of the Study Treatment period. Study treatment for the Single-Agent QD Arm will consist of repeated 28-day cycles of oral MLN0128 milled API capsules taken on an empty stomach. The first 6 patients enrolled into the Single-Agent QD Arm Study Treatment period will receive MLN0128 at 4 mg QD. An evaluation of safety and tolerability will be conducted after these first 6 patients have completed Cycle 1 to determine the dose to be administered during the Study Treatment period for the next patients enrolled into the Single-Agent QD Arm. Safety evaluations will continue before enrolling each subsequent cohort into the Single-Agent QD Arm. A total of 16 patients will complete the protocol-specified PK evaluations in the Single-Agent QD Arm.

The Combination Arm will test the safety, tolerability, and PK of MLN0128 milled API capsules when administered on an empty stomach in combination with paclitaxel. Paclitaxel (80 mg/m^2) will be administered as an IV infusion on Days 1, 8 (± 1 day), and 15 (± 1 day) of each 28-day cycle according to the institution's standard clinical practice. MLN0128 will be administered QD × 3 days QW of each cycle, beginning 24 hours after completion of the Day 1 paclitaxel infusion; ie, MLN0128 will be administered on Days 2 through 4, 9 through 11, 16 through 18, and 23 through 25 of every 28-day cycle. The starting MLN0128 dose for the Combination Arm will be 6 mg (QD × 3 days QW). Plasma samples to characterize the PK of MLN0128 will be collected on Cycle 1 Day 2.

Consistent with the Single-Agent QD Arm, an interim safety and tolerability review will be conducted for the Combination Arm after the initial cohort of 6 patients has completed Cycle 1. According to standard dose escalation rules, on the basis of the safety and tolerability observed in the initial 6 evaluable patients, the dose of MLN0128 (QD × 3 days QW) for the next cohort of 6 patients will be either reduced, maintained, or escalated.

The Single-Agent QW Arm will evaluate the safety, tolerability, and PK of MLN0128 milled API when administered on an empty stomach in 2 sequential cohorts, each consisting

of 6 to 12 patients. Initially, 6 patients in Cohort 1 will receive 20 mg of MLN0128 capsules based on milled API once every week (QW). Serial plasma specimens will be collected for evaluation of MLN0128 PK. A safety and tolerability assessment will be performed after the last patient in the cohort completes Cycle 1. If ≥2 patients experience a dose-limiting toxicity (DLT) during Cycle 1, then the starting dose of MLN0128 milled API for the subsequent cohort (Cohort 2) will be reduced to 15 mg QW. If ≤1 patient in Cohort 1 experiences a DLT in Cycle 1, then the dose of milled MLN0128 in Cohort 2 will be increased to 30 mg QW. If the dose of MLN0128 milled API is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to 12 patients to confirm the RP2D for single-agent MLN0128 milled API capsules when administered QW.

Blood will be collected from all patients for PK analysis of MLN0128. Throughout the study, patient safety will be monitored through assessment of AEs clinical laboratory values, vital signs, and electrocardiograms (ECGs). Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.

1.2   Study Objectives

1.2.1 Primary Objectives

- To evaluate the safety and tolerability of MLN0128 milled API capsules administered both as a single agent and in combination with paclitaxel

- To characterize the effect of a high-fat meal on the PK of MLN0128 milled API capsules

- To characterize the PK of MLN0128 milled API capsules when administered on an empty stomach approximately 24 hours after paclitaxel infusion

1.2.2 Secondary Objectives

- To characterize the PK of MLN0128 milled API capsules versus unmilled API capsules, when administered on an empty stomach

- To evaluate the preliminary efficacy of MLN0128 milled API capsules when administered as a single agent and in combination with paclitaxel

2.   POPULATIONS FOR ANALYSIS

2.1   Safety Population

The safety population includes all patients who receive at least 1 dose of study drug, and will be used for all safety and efficacy analyses.

2.2   Pharmacokinetics Population

The pharmacokinetics population includes patients with protocol specified dosing and conditions and PK data to reliably estimate PK parameters and will be used for all PK analyses.

2.3   DLT Evaluable Population

The DLT evaluable population is defined as patients who received 75% or more of planned doses of MLN0128 in Cycle 1 or stopped study drug before receiving 75% of planned doses because of study drug related AE (considered as a DLT). Patients who receive at least 75% (21 of 28 for QD dosing schedule; 3 of 4 for QW dosing schedule; 9 of 12 for QDx3d QW dosing schedule) of the planned doses in Cycle 1 will be considered to have sufficient safety data/follow-up to support dose escalation. Patients who receive less than 75% of the planned doses in the first cycle of treatment for reasons unrelated to study drug toxicity will be considered to have inadequate data to support dose escalation.

3.   HYPOTHESES AND DECISION RULES

Not applicable.

4.   INTERIM ANALYSIS

Not applicable.

5.   STATISTICAL METHODOLOGY

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent (of nonmissing) per category for categorical data, unless specified otherwise.

Data will be summarized by dose level [ordered] for each arm:

Single-Agent QD Arm

MLN0128 4 mg QD	MLN0128 *TBD* mg QD	Total

Single-Agent QD Arm: Adverse event tables

PK Run-In MLN0128 4 mg x 3 doses	MLN0128 4 mg QD	MLN0128 *TBD* mg QD	Total

Combination Arm:

MLN0128 6 mg QDx3 + Paclitaxel 80 mg/m2	MLN0128 *TBD* mg QDx3 + Paclitaxel 80 mg/m2	Total

Single-Agent QW Arm:

MLN0128 30 mg QW	MLN0128 *TBD* mg QW	Total

5.1 Sample Size Justification

The within-patient coefficient of variation for AUC0-last was estimated to be 39% on the basis of preliminary PK data from Cycle 1 Day 1 and Cycle 2 Day 1 from Study INK128-001. Assuming a geometric mean AUC ratio of 1, with a sample size of 16, the 2-sided 90% CI for the geometric mean AUC ratio is expected to be (0.796, 1.257). On the basis of these calculations, a sample size of 16 patients completing the protocol specified PK evaluations in the Single-Agent Arm has been selected to enable adequate precision in the estimation of the geometric mean ratios.

In the Combination Arm, 6 patients will be enrolled in the first cohort (6 mg QD × 3 days QW), and another 6 patients will be enrolled in the second cohort (either 4 mg QD × 3 days QW or 8 mg QD × 3 days QW). Any cohort may be expanded up to 12 patients for confirmation of RP2Ds for MLN0128 milled API capsules when administered QD × 3 days QW in combination with paclitaxel. The number of patients is based on clinical considerations.

For the Single-Agent QW Arm, 6 patients will be enrolled in the first cohort (20 mg QW), and another 6 patients will be enrolled in the second cohort (either 15 or 30 mg QW). Any cohort may be expanded up to 12 patients for confirmation of RP2Ds for MLN0128 milled API capsules when administered QW. The number of patients is based on clinical considerations.

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 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.

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 in the Single-Agent QD Arm who are withdrawn from treatment before completing per-protocol PK assessments in the PK Run-In period will be replaced. In addition, patients in the Single-Agent QD Arm who miss a dose or experience emesis within 8 hours of dosing before completing per-protocol PK assessments in the PK Run-In period will be replaced (but not removed from treatment) to achieve a sample size of 16 patients completing the protocol-specified PK evaluations . Patients in all treatment arms who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced.

5.5   **Patient Disposition**

The number of patients screened, in the safety population, in the PK population, in the DLT evaluable population, and the reason study drug was discontinued will be summarized. All percentages will be based on the number of patients in the safety population.

A listing with date of first dose, date of last dose, number of cycles, reason for discontinuation of study treatment, and study populations will be generated.

5.6   **Demographics and Baseline Disease Characteristics**

Listings with demographic, disease characteristics, prior therapy, radiation, and surgery will be generated.

5.6.1   **Demographics**

The following demographic characteristics will be summarized: age at date of informed consent, sex, ethnicity, race, baseline weight, and height.

5.6.2   **Medical History**

5.6.2.1   **Disease-Specific History**

The following will be summarized:

- Baseline ECOG performance status
- Primary diagnosis
- Years since first positive biopsy
- Stage of disease at initial diagnosis

The number and percentage of patients with prior surgery, prior radiation, and prior systemic anticancer therapies will be summarized.   The following will be summarized for those patients with prior systemic therapies:

- Systemic regimen received (WHO generic name)
- Number of prior systemic treatment regimens
- Setting of most recent systemic treatment
- Best response to most recent systemic treatment
- Reason most recent systemic treatment discontinued

5.7 Treatments and Medications

5.7.1 Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO generic name.

5.7.2 Study Treatments

In the Single-Agent QD arm each patient will receive a total of three 4-mg doses of MLN0128 during the PK Run-In period at least 48 hours apart. Following the PK Run-In period, single-arm QD patients will receive repeated 28-day cycles of oral MLN0128 milled API capsules taken on an empty stomach. The first 6 patients enrolled into the Single-Agent Arm will receive MLN0128 at 4 mg QD. Further cohorts will receive either 3 mg QD or 5 mg QD.

In the Combination Arm, paclitaxel (80 mg/m^2) will be administered as an IV infusion on Days 1, 8 ($\pm$ 1 day), and 15 ($\pm$ 1 day) of each 28-day cycle. MLN0128 will be administered QD × 3 days QW of each cycle, beginning 24 hours after completion of the Day 1 paclitaxel infusion; ie, MLN0128 will be administered on Days 2 through 4, 9 through 11, 16 through 18, and 23 through 25 of every 28-day cycle. The starting MLN0128 dose for the Combination Arm will be 6 mg QD × 3 days QW. Further cohorts will receive either 4 mg QD × 3 days QW or 8 mg QD × 3 days QW.

In the Single-Agent QW arm patients will receive repeated 28-day cycles of oral MLN0128 milled API capsules taken on an empty stomach. The first 6 patients enrolled into the Single-Agent Arm QW arm receive MLN0128 at 20 mg QW. Further cohorts will receive either 15 mg QW or 30 mg QW.

5.7.2.1 Extent of Exposure

The overall treatment duration in weeks (date of last dose – date of first dose + 1/ 7), total number of cycles administered (distribution and summary statistics), cumulative dose, dose per administration (cumulative dose divided by the total number of doses taken) and the percentage of planned original dose will be summarized. For patients in the single-agent QD arm participating in the PK run-in period the treatment duration will be based on the first dose of MLN0128 during the PK run-in period.

The percentage of planned original dose is calculated as the cumulative dose taken (mg for MLN0128 and mg/m^2 for paclitaxel) divided by the total planned dose (mg for MLN0128 and mg/m^2 for paclitaxel). The total planned dose is:

Assigned dose level at study start * doses per cycle * maximum number of cycles.

In the single-Agent QD arm there are 28 planned MLN0128 doses per cycle and 3 MLN0128 doses planned during the PK run-in period, in the Combination with Paclitaxel arm there are 12 planned MLN0128 planned doses per cycle, and in the Single-Agent QW arm there are 4 planned MLN0128 doses per cycle. In the Combination with Paclitaxel arm there are 12 planned paclitaxel doses per cycle.

The number and percentage of patients will be summarized for the following actions on study drug:

- MLN0128 Dose Reduced at Least Once
- MLN0128 Dose Interrupted due to Adverse Event at Least Once
- MLN0128 Dose Interrupted due to Dosing Error at Least Once
- MLN0128 Dose Interrupted due to Other Reasons at Least Once

For the single-agent QD arm any actions on study drug that occur during the PK run-in period will be included in the above summaries. For the Combination with paclitaxel arm similar summaries will be provided for paclitaxel.

A listing with study drug administration results for MLN0128 and paclitaxel as collected on the eCRF, including timing of action on study drug will be generated.

5.8   Efficacy Analyses

The best overall response, objective response rate (CR+ PR), and clinical benefit rate (CR + PR + SD, and CR + PR + SD of at least 6 months) will be summarized.

The duration of stable disease will be calculated for those patients with a best response of stable disease. The duration of SD is the number of days from cycle 1 day 1 until progressive disease or until the last response assessment if there is no progressive disease.

The duration of objective response will be calculated for those patients with a best response of CR or PR, and is defined as the number of days from the start date of CR, or PR (whichever response is achieved first) until progressive disease or until the last response assessment if there is no progressive disease.

Data listings will present the tumor measurements from CT or MRI, change/percent change from baseline in sum of the longest diameter (SLD), change/percent change from nadir in

SLD, non-target disease assessment, new lesion assessment and disease response assessment by the investigator based on RECIST criteria at each response assessment. In addition, the best overall response, duration of SD, and duration of objective response will be presented in a data listing.

5.9   Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

5.9.1   Pharmacokinetic Analyses

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

Pharmacokinetic Concentrations

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum, and maximum) will be used to summarize the plasma concentrations. 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.

Linear and semi-logarithmic plots of the mean plasma concentration versus scheduled sampling time will be provided for the following:
1. Single- agent QD arm for treatment state (combination of dosing condition and MLN0128 API capsules) during the PK-run in period:
   - MLN0128 unmilled API capsules taken on an empty stomach
   - MLN0128 milled API capsules following a high-fat meal
   - MLN0128 milled API capsules taken on an empty stomach
2. Single-agent QW arm by dose level
3. Combination with Paclitaxel arm by dose level

Linear and semi-logarithmic plots of individual plasma concentration versus actual sampling time will be provided as described above. All individual patient plasma concentration data will be in a data listing.

Pharmacokinetic Parameters

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.

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 presented. All individual patient PK parameter data will be in a data listing.

Descriptive statistics will be presented for the plasma PK parameters listed below for each treatment state (combination of dosing condition and MLN0128 API capsules) during the PK-run in period (MLN0128 unmilled API capsules taken on an empty stomach, MLN0128 milled API capsules following a high-fat meal, and MLN0128 milled API capsules taken on an empty stomach) and by dose level for the Single-Agent QW and Combination with Paclitaxel arm.

Data permitting, the following single-dose PK parameters will be calculated for MLN0128 by noncompartmental analysis:

- Area under the plasma concentration-time curve from time 0 to time of last measurable concentration (AUC_{0-last})
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{0-inf})
- Area under the plasma concentration-time curve from time 0 to 24 hr ($AUC24hr$)
- Area under the plasma concentration-time curve from time 0 to 8 hr ($AUC8hr$) [combination with paclitaxel arm only]
- Observed maximum plasma concentration (Cmax)
- Time to observed maximum plasma concentration (Tmax)
- Terminal disposition phase rate constant (lambdaz)
- Terminal phase phase half-life (t1/2)
- Apparent oral clearance (CL/F)
- Apparent terminal phase volume of distribution (Vz/F)

For the single-agent QD arm an analysis of variance will be performed for the log-transformed C_{max} and AUC_{0-last} as the dependent variables, treatment state as the fixed effect, and patient as the random effect. Least-square mean ratios between the treatment states

MLN0128 dosed with high-fat breakfast [Test]) versus MLN0128 dosed on an empty stomach [Reference]) and MLN0128 milled API capsules [Test] versus MLN0128 unmilled API capsules [Reference] will be calculated along with 90% confidence intervals (CIs).

5.9.2   Pharmacodynamic Analyses

CCI

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 physical examination, vision examination, 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

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.

Treatment emergent adverse events are defined as adverse events that start on or after the first dose of study drug and less than or equal to 30 days after the last dose of study drug. The reported adverse event term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in use at the time of database lock (v17.0 or higher).

Adverse events 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 event will be considered treatment-emergent if both the month and year of the start date of the event 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 event will be considered treatment -emergent if the year of the start date of the event 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 event is completely missing, then the event is assumed to be treatment-emergent.

Treatment emergent adverse events will be summarized based on the number and percentage of patients experiencing events by MedDRA system organ class and preferred term. Tabular summaries by system organ class and preferred term will be provided for the following:

- All TEAEs
- TEAEs related to Study Drug
- Grade 3 or greater TEAEs
- Grade 3 or greater TEAEs related to Study Drug
- Most common (at least 10% in each arm) (by preferred term)
- Most common (at least 10% in each arm) TEAEs by maximum grade and preferred term

In the Combination with Paclitaxel arm related to study drug refers to either MLN0128 or paclitaxel.   For the MLN1028 Single-Agent QD arm, AEs starting that start during the PK-run in period will be summarized separately.   Patients reporting the same event more than once will have that event counted only once within each body system, and once within each preferred term.

A listing of patients with a DLT in Cycle 1, and all treatment-emergent adverse events will be provided.

Adverse events of interest will be tabulated for the following:

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

Adverse event of interest	MedDRA Preferred Term
Asthenic Conditions	Asthenia, Fatigue, Lethargy, Listless, Malaise, Sluggishness, Muscle Weakness

5.10.1.2 Serious Adverse Events

The number and percentage of patients experiencing treatment-emergent serious AEs (SAE) and treatment-emergent study drug related SAE will be summarized by MedDRA primary system organ class, and preferred term.

In addition, a by-patient listing of the SAEs will be presented.

5.10.1.3 Deaths

A by-patient listing of deaths within 30 days of last dose of study drug based on adverse events with an outcome of fatal will be presented.

5.10.1.4 Adverse Events Resulting in Discontinuation of Study Drug

The following listings will be generated:

- TEAEs resulting in discontinuation of study drug [action taken= drug withdrawn]
- TEAEs resulting in reduction or interruption of study drug [action taken=dose interrupted or action taken=dose reduced]

In the Combination with Paclitaxel arm study drug refers to either MLN0128 or paclitaxel.

5.10.2 Laboratory Data

For the purposes of summarization, all laboratory values will be converted to standardized units. Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.0. The NCI CTCAE version 4.0.3 toxicity criteria for creatinine will be modified to exclude the comparison to baseline. The number and proportion of patients with shifts in NCI CTCAE toxicity grades relative to the baseline toxicity grade will be summarized. For those laboratory tests not assigned NCI-CTCAE toxicity grades the number and proportion of patients with shifts in laboratory values to outside the laboratory normal range relative to the baseline value will be summarized.

5.10.3   **Vital Signs and Weight**

Vital sign results (diastolic and systolic blood pressure) and body weight will be summarized 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.

5.10.4   **Electrocardiograms**

For the subset of patients enrolled under amendment #2 with pre-dose and 2 hour post-dose ECGs performed on Day 1 of each cycle the minimum and maximum 2 hour post dose values will be summarized for each ECG parameter (ventricular rate, PR, QRS, QT, and QTc (Fridericia) . The pre-dose value and the change from the pre-dose to the minimum and maximum 2 hour value will also be summarized. For the maximum change from pre-dose in QT/QTc interval the number and percent of patients with increases >30 ms and >60 ms will also be summarized.

All QT values will be converted to QTcF using Fridericia's correction:

$$QT_F = \frac{QT}{\sqrt[3]{RR}} \text{(sec)}$$

[Note: convert RR recorded on ECG CRF from msec to sec, if the RR is not available use: 60 seconds divided by the ventricular rate in beats/minute].

5.10.5   **ECOG Performance Status**

ECOG performance status scores will be summarized in the same manner as described for vital signs in section 5.10.3 (maximum post-baseline only).

6.   **CHANGES TO PLANNED ANALYSES FROM PROTOCOL**

Reference materials for this statistical plan include Clinical Study Protocol MLN0128-1004 Amendment 2 dated 14May2105 and the accompanying data collection Case Report Form version 1.0 dated 06Mar2015.

7.   **PROGRAMMING CONSIDERATIONS**

7.1   **Statistical Software**

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

7.2   **Rules and Definitions**

Populations are defined in Section 2.

Treatment-emergent AEs are defined in Section 5.10.1.1.