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

NCT Number: NCT02197572

Protocol Approve Date: 28 November 2017

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CLINICAL STUDY PROTOCOL C31002 PROTOCOL AMENDMENT 2

MLN0128

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

Protocol Number:	C31002
Indication:	Advanced solid tumors
Phase:	1
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	Not applicable
Therapeutic Area:	Oncology

Protocol History

Original	29 October 2013
Protocol Amendment 1	26 June 2014
Protocol Amendment 2	28 November 2017

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Note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as: "millennium", "Sponsor" or "Takeda."

Approved by:

Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

PPD

Signature *Date DD Month YYYY*

Protocol Amendment 2 Summary of Changes

Rationale for Amendment 2

This document describes the changes in reference to the protocol incorporating Amendment 2. The primary purpose of this amendment is to update those sections affected by new nonclinical data for MLN0128 metabolism by specific cytochrome P450 (CYP) isoforms. The study's exclusion criteria, list of prohibited concomitant medications, description of potential drug-drug interactions, list of relevant CYP inhibitors, and dietary restrictions related to CYP inhibitors and inducers have been updated accordingly. The required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment has also been reduced.

Minor grammatical, editorial and formatting changes are included for clarification purposes only.

For specific examples of changes in text and where the changes are located, see Section 14.6.

The purposes of this amendment are to:

1. Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.
2. Update the list of concomitant medications prohibited during the study.
3. Update the description of potential drug-drug interactions.
4. Update the list of relevant CYP inhibitors and inducers.
5. Remove the dietary restrictions related to CYP inhibitors and inducers.
6. Insert language to reduce the required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment per protocol.

PROTOCOL SUMMARY

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

Number of Patients: Approximately 30 patients will be enrolled in this study.

Study Objectives

Primary

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

Secondary

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

Overview of 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 QT/QTc interval in patients with advanced solid tumors. The study will enable collection of time-matched pharmacokinetic (PK) and electrocardiogram (ECG) data before and after MLN0128 administration at the time points specified in the Schedule of Events. A central ECG reader will be used and continuous 12-lead digital ECGs will be obtained using a Holter H12+ ECG recorder. All planned 12-lead ECG collections will be obtained in triplicate.

On the morning of Screening; Day -1 baseline measurements of serial triplicate ECGs (0-10 hours) will be obtained. Three Holter ECGs will be extracted at the time points that match the Cycle 1, Day 1 PK/ECG sampling times. The clock time of ECG assessments on Screening; Day -1 should coincide with the clock time of PK/ECG assessments for Cycle 1, Day 1. After collection of the planned 10-hour ECG sample on Cycle 1, Day 1, the Holter recorders will not be removed and patients will be furloughed from the study site.

On Screening; Day -1 and Cycle 1, Day 1, patients will be given the option to report to the site fasted or after having a light morning meal as long as the meal has been completed at least 2 hours before the scheduled baseline triplicate ECG on each day. If patients report to the site fasted, they should do so with adequate time (approximately 3 hours before the scheduled baseline triplicate ECG) in order to eat a light, standard breakfast provided by the site that will need to be completed at least 2 hours before the scheduled baseline triplicate ECG on each day. Patients will be instructed not to eat for the next 6 hours (ie, 2 hours before the 0-hour, predose time point and until completion of the collection of the 4-hour postdose PK/ECG assessments). Light meals will be administered at the same time on Screening; Day -1 and Cycle 1, Day 1.

In addition, all patients will be issued a glucometer and trained to use it to monitor their daily predose fasting blood glucose (FBG) levels at home for the days on which glucose is not measured at the clinic. Patients will be instructed to notify the study staff immediately with any abnormal readings (ie, $\geq$ 150 mg/dL) for further instructions on the management of hyperglycemia. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

To mitigate nausea and vomiting known to occur at a 40 mg dose of MLN0128, patients will be administered an antiemetic agent (0.25 mg palonosetron) on Cycle 1, Day 1.

After collection of the 10-hour postdose PK/ECG assessment on Cycle 1, Day 1, patients will be furloughed from the study site. The Holter recorders will not be removed during this furlough

period.

On Cycle 1, Day 2 and Cycle 1, Day 3, patients may eat and drink up to approximately 2 hours before arriving at the study site for PK/ECG evaluations.

On Cycle 1, Day 2, patients will report to the clinical facility at least 1 hour before the 24-hour postdose PK/ECG (triplicate) assessments. After the PK/ECG assessments are completed, the Holter recorders will be removed and patients will be furloughed from the study site.

On Cycle 1, Day 3, patients will report to the clinical facility at least 1 hour before the 48-hour postdose assessments, which will represent the final study endpoint-specific planned PK/ECG assessments.

After completing the PK/ECG assessments on Cycle 1, Day 3, patients may continue to receive MLN0128 if, in the opinion of the investigator, the patient is deriving clinical benefit, until they experience disease progression. Patients continuing treatment with MLN0128 at the discretion of the investigator will receive a dose of MLN0128 up to 30 mg every week (QW). Dose escalation will not be permitted, and a maximum of 2 dose reductions (for patients experiencing study drug-related toxicity) will be permitted. Patients will return to the study site for follow-up visits at the time points in the Schedule of Events. Treatment may continue until disease progression, unacceptable MLN0128-related toxicity, withdrawal of consent, or for up to 12 months (whichever occurs first). All patients enrolled in the study will attend the End of Study/Early Termination visit 30 (to 40) days after receiving their last dose of study drug.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (AEs), Version 4.03, effective date 14 June 2010. AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of MLN0128.

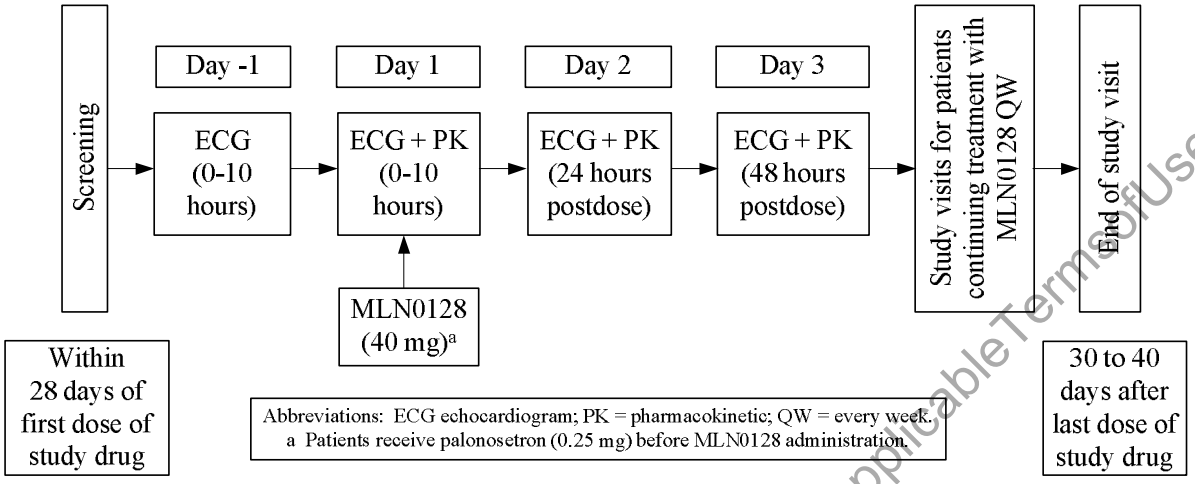
Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) will be obtained at baseline and Cycle 3, Day 28, after which point CT (with contrast) or MRI may be performed every 3 cycles at the investigator's discretion as clinically indicated, according to standard of care.

Study Population: Men or women 18 years or older with a radiographically or clinically evaluable solid tumor for which standard-of-care therapy has failed may be enrolled in this study; however, measurable disease as defined by modified Response Evaluation Criteria in Solid Tumors criteria is not required. Patients with a history of brain metastasis may be eligible provided all of the following criteria are met: treated brain metastases; no evidence of disease progression or hemorrhage after treatment; off-treatment with dexamethasone for 28 days before administration of the first dose of MLN0128; and no ongoing requirement for dexamethasone or anti-epileptic drugs. Eligible patients must have an Eastern Cooperative Oncology Group performance status of 0 or 1 and the following clinical laboratory values within 28 days before the first dose of MLN0128: total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN); alanine aminotransferase and aspartate aminotransferase $\leq 2.5 \times$ the ULN; creatinine clearance ≥ 50 mL/min; absolute neutrophil count $\geq 1.5\times10^9$/L; platelet count $\geq 100\times10^9$/L; hemoglobin ≥ 10 g/dL; fasting glucose ≤ 120 mg/dL and fasting triglycerides ≤ 300 mg/dL. Left ventricular ejection fraction must be within 5 absolute percentage points of institutional standard of normal within 28 days before the first dose of MLN0128.

Patients with a history of leptomeningeal disease or spinal cord compression or tumors with involvement of the mediastinum are not eligible. Patients with a diagnosis of diabetes mellitus may not be enrolled in the study. Patients with a history of any of the following within 6 months before study entry are also not eligible: ischemic myocardial event; ischemic cerebrovascular event; requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia

(including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia); a pacemaker for control of rhythm; New York Heart Association Class III or IV heart failure; or pulmonary embolism. Additionally, patients are not eligible if they have significant active cardiovascular or pulmonary disease at study entry, including: uncontrolled high blood pressure (ie, systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg); resting pulse rate of < 50 beats per minute or > 100 beats per minute at screening or predose; pulmonary hypertension; uncontrolled asthma or O_2 saturation < 90%; significant valvular disease; severe regurgitation or stenosis, or history of valve replacement; medically significant (symptomatic) bradycardia; history of arrhythmia requiring an implantable cardiac defibrillator; requirement for QT-prolonging drugs with a risk of causing torsades de pointes (TdP). Patients with a baseline prolongation of QTc (rate-corrected QT interval [msec] of electrocardiograph with Fridericia correction [QTcF] > 430 msec for men and QTcF > 450 ms for women), TdP, Brugada syndrome, or a history of thoracic surgery or congenital long QT syndrome (LQTS; or family history of LQTS) are not eligible for enrollment in this study.
Duration of Study: It is anticipated that this study will last for approximately 12 months.

STUDY OVERVIEW DIAGRAM



SCHEDULE OF EVENTS

	Screening[a]	Treatment Cycles											EOS/ Early termination[b]
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5 and beyond		
	Day -28 to Day-1	Day 1	Day 2 (24hr postdose)	Day 3 (48hr postdose)	Day 15 (±2 days)	Day 1	Day 15 (±2 days)	Day 1	Day 28 (-7 days)	Day 1	Day 1	Day 28 (-7 days)	
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history	X												
Physical examination	X	X	X	X	X	X	X	X		X	X		X
Height	X												
Weight	X	X	X	X	X	X	X	X		X	X		X
Vital signs[c]	X	X	X	X	X	X	X	X		X	X		X
ECOG performance status	X	X				X		X		X	X		
MUGA/ECHO	X												
Single, 12-lead ECG	X	X[d]											X
Serial, triplicate ECGs for continuous 12-lead ECG Holter monitoring[e]	X	X	X	X									
Disease assessment[f]	X								X			Q3C[f]	

	Screening[a]	Treatment Cycles											EOS/ Early term-ination[b]
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5 and beyond		
	Day -28 to Day-1	Day 1	Day 2 (24hr postdose)	Day 3 (48hr postdose)	Day 15 (±2 days)	Day 1	Day 15 (±2 days)	Day 1	Day 28 (-7 days)	Day 1	Day 1	Day 28 (-7 days)	
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug.											
	Serious adverse events[g] will be reported from signing of the informed consent form through 30 days after the last dose of study drug.												
MLN0128 administration		QW dosing (see Section 6.1)[h]											
Antiemetic administration[i]		X											
Samples/Laboratory Assessments													
Pregnancy test[j]	X1	X1											
Hematology/ chemistry[k]	X1	X1			X1	X1	X1	X1		X1	X1		X1
Urinalysis	X1[l]	X1			X1	X1	X1	X1		X1	X1		X1
Fasting glucose[m]	X1	X				X1		X1		X1	X1		X1
In-home daily fasting glucose monitoring[n]			X										
Fasting lipid profile	X1[o]							X1		X1	X1		X1
HbA1c	X1							X1			Q3C		
Blood samples for PK[p]		X12	X1	X1									

	Screening[a]	Treatment Cycles											EOS/ Early termination[b]
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5 and beyond		
	Day -28 to Day-1	Day 1	Day 2 (24hr postdose)	Day 3 (48hr postdose)	Day 15 (±2 days)	Day 1	Day 15 (±2 days)	Day 1	Day 28 (-7 days)	Day 1	Day 1	Day 28 (-7 days)	

Abbreviations: β-hCG = beta-human chorionic gonadotropin; CBC = complete blood count; CT = computed tomography; CXDX = Cycle X, Day X; ECHO = echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; HbA1c = glycosylated hemoglobin; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition (scan); PK = pharmacokinetic; Q3C = every 3 cycles; QW = every week; WBC = white blood cell; X# = number of samples required (eg, two samples = X2).

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 days) with permission of the project clinician for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.**

a Screening assessments are performed within 28 days before the C1D1 MLN0128 dose. Screening assessments performed no more than 3 days before Screening; Day -1 will qualify as baseline assessments and need not be repeated, unless otherwise specified. Screening; Day -1 is defined as the day before first dose of study drug; screening assessments must be completed by Screening; Day -1.

b Patients will attend an EOS/Early Termination visit 30 to 40 days after receiving their last dose of MLN0128.

c Vital sign measurements include blood pressure (diastolic and systolic), heart rate, and temperature.

d The C1D1 single, 12-lead ECG can be collected 2-4 hours after dosing.

e When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample.

f Baseline CT (with contrast) or MRI scan of the chest, abdomen, and pelvis must be obtained within 4 weeks before the first dose of MLN0128 and at C3D28, after which point CT (with contrast) or MRI may be performed Q3C (ie, C6D28, C9D28, C12D28, etc) as clinically indicated, according to standard of care. The same imaging modality (CT [with contrast] or MRI) should be used throughout the study. Scans are permitted up to 7 days in advance of the study visit. For long term patients, defined as study participation (≥ 1 year, a CT (with contrast)/MRI of chest, abdomen, and pelvis will be obtained at intervals of up to every 4 cycles (plus or minus 7 days) as clinically indicated.

g Including serious pretreatment events; see Section 9.1.1 for definition.

h A single dose of 40 mg MLN0128 will be administered on C1D1; patients continuing treatment with MLN0128 after C1D3 at the discretion of the investigator will receive a maximum dose of 30 mg MLN0128 administered on a QW schedule.

i Patients will be administered an antiemetic agent (0.25 mg palonosetron) as an intravenous infusion over 30 seconds, at least 30 minutes before study drug administration.

j A serum β-hCG pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of MLN0128 is administered (ie, within the 4 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an independent ethics committee/institutional review board, or if required by local regulations.

	Screening[a]	Treatment Cycles											EOS/ Early term-ination[b]
		Cycle 1				Cycle 2		Cycle 3		Cycle 4	Cycle 5 and beyond		
	Day -28 to Day-1	Day 1	Day 2 (24hr postdose)	Day 3 (48hr postdose)	Day 15 (±2 days)	Day 1	Day 15 (±2 days)	Day 1	Day 28 (-7 days)	Day 1	Day 1	Day 28 (-7 days)	

k The hematology and chemistry blood samples for C1D1 may be collected within 4 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 4 days before the C1D1 dose, it need not be repeated on C1D1. For all other visits, assessments may be performed ≤ 24 hours before the study visit. Hematology includes CBC with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBC), differential WBC count, neutrophils, and platelets. Machine counts are acceptable. The chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma glutamyl transferase, albumin, glucose, urate, calcium, phosphate, and magnesium.

l For screening, creatinine clearance must be ≥ 50 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.

m Fasting glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements, beginning Cycle 1, Day 4; see 7.4.16 for fasting requirements.

n Patients will be given a glucometer on C1D1 to monitor daily fasting glucose levels at home and will be instructed to notify the study clinician when the fasting glucose is abnormal (ie, ≥ 150 mg/dL). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See Section 7.4.18 for further instruction.

o To be completed within 14 days of C1D1 dosing. See Section 7.4.15 for further instruction.

p Blood samples for PK analysis will be obtained according to the schedule presented in the Pharmacokinetic Sample Breakdown.

PHARMACOKINETIC SAMPLE BREAKDOWN

	Screening		Cycle 1					
	Day -1		Day 1[b]		Day 2		Day 3	
	Triplicate ECG[a]	PK	Triplicate ECG[a]	PK	Triplicate ECG[a]	PK	Triplicate ECG[a]	PK
Predose (On C1D1: ≤ 15 min before dosing)	X		X	X				
0.25 hour postdose (± 5 min)	X		X	X				
0.5 hour postdose (± 5 min)	X		X	X				
1 hour postdose (± 15 min)	X		X	X				
1.5 hours postdose (± 15 min)	X		X	X				
2 hours postdose (± 15 min)	X		X	X				
2.5 hours postdose (± 15 min)	X		X	X				
3 hours postdose (± 30 min)	X		X	X				
4 hours postdose (± 45 min)	X		X	X				
6 hours postdose (± 45 min)	X		X	X				
8 hours postdose (± 1 hour)	X		X	X				
10 hours postdose (± 1 hour)	X		X	X				
24 hours postdose (± 1 hour)					X	X		
48 hours postdose (± 1 hour)							X	X

Abbreviations: CxDx = Cycle x, Day x; ECG = electrocardiogram; PK = pharmacokinetic(s).

When the timing of a blood sample for PK or safety laboratory analysis coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. The triplicate ECG measurements should be completed immediately before the corresponding blood sample for PK or safety laboratory analysis.
See Section 7.4.16 for information regarding fasting periods that are required in advance of PK/ECG testing.

a Holter monitors will be used to collect triplicate ECG measurements. Holter ECG measurements will be performed over the course of 15 minutes (at least 5 min supine prior to the first ECG measurement, and then a 10-minute period of extracting the triplicate ECG measurements at approximately 2- to 5-minute intervals). Timing of ECG collection on Screening; Day -1 should match PK/ECG collection on C1D1 to enable appropriate baseline correction.

b MLN0128 will be administered to patients at the clinic on C1D1. If a patient is deemed not evaluable by the sponsor, the postdose C1D1 Holter ECG monitoring and PK sampling procedures need not be performed. Refer to Section 7.6 for additional information.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
4E-BP1	eukaryotic initiation factor 4-binding protein
AE	adverse event
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
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
BCRP	breast cancer-resistant protein
C_{max}	single-dose maximum (peak) concentration
CT	computed tomography
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
ER	estrogen receptor
ER+/HER2−	estrogen receptor positive/human epidermal growth factor receptor-2 negative
FBG	fasting blood glucose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	Gastrointestinal
hERG	human ether-à-go-go related gene
HDPE	high-density polyethylene
HER2	human epidermal growth factor receptor 2
IB	Investigator's Brochure
IC	informed consent

Abbreviation	Term
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
LQTS	long QT syndrome
LVEF	left ventricular ejection fraction
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian (or mechanistic) target of rapamycin
MUGA	multiple gated acquisition (scan)
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	progesterone receptor
QD	*quaque die*; every day; once daily
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
QTc	rate-corrected QT interval (millisec)
QTcB	rate-corrected QT interval (millisec) with Bazett correction
QTcF	rate-corrected QT interval (millisec) Fridericia correction
QTcI	individual baseline corrected rate-corrected QT interval (millisec)
QW	every week; once weekly
S473	Serine 473
S6K	ribosomal protein S6 kinase
SAE	serious adverse event
$t_{1/2}$	terminal disposition half-life
T308	Threonine 308
TdP	torsades de pointes
TEAE	treatment-emergent adverse events

Abbreviation	Term
T_{max}	single-dose first time of occurrence of maximum (peak) concentration
TORC1	mammalian (or mechanistic) target of rapamycin complex 1
TORC2	mammalian (or mechanistic) target of rapamycin complex 2
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

The mammalian (or mechanistic) target of rapamycin (mTOR) is a central regulator of cell growth, metabolism, and angiogenesis that functions in 2 distinct multiprotein complexes, mTOR complex 1 (TORC1) and mTOR complex 2 (TORC2). Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of TORC1, but only partially inhibit TORC1 substrates. They do not directly inhibit TORC2, which has shown to be an emerging target in cancer research. MLN0128 is a novel selective, orally bioavailable mTOR inhibitor that targets both TORC1 and TORC2, which may lead to increased antitumor activity.

1.1.2 Study Drug

mTOR Inhibitors

The mTOR serine/threonine kinase has a central role in regulating cellular growth and metabolism in response to external environmental factors.[1, 2] The mTOR kinase binds with other proteins to form 2 distinct multiprotein complexes, TORC1 and TORC2. The TORC1 complex is stimulated by growth factors and amino acids and regulates cell growth by controlling the activity of the ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4-binding protein (4E-BP1).[3] The TORC2 complex is activated by growth factors and promotes cell survival, proliferation, and actin cytoskeleton organization by phosphorylating and activating kinases, such as serine/threonine-specific protein kinase (AKT; also known as protein kinase B), which is a regulator of apoptosis.[4, 5]

Two major classes of mTOR inhibitors are under development: allosteric inhibitors and adenosine triphosphate (ATP)-competitive inhibitors. The first-generation, or allosteric, inhibitors include rapamycin and the related analogs or rapalogs temsirolimus, everolimus, and ridaforolimus. The rapalogs effectively inhibit phosphorylation of S6K but only partially inhibit the phosphorylation of 4E-BP1, which regulates cap-dependent translation of transcripts for cell survival, proliferation, and angiogenesis.[2] Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1.[2]

The ATP-competitive inhibitors (also known as mTOR kinase inhibitors or TORKinibs), such as MLN0128, bind to the catalytic domain of mTOR and thus inhibit both TORC1 and

TORC2 complexes, including the rapamycin-insensitive or -resistant actions of TORC1, such as phosphorylation of 4E-BP1.[6, 7, 8]

The rapalogs temsirolimus and everolimus have been approved by the United States (US) Food and Drug Administration (FDA) as monotherapy for patients with advanced renal cell carcinoma (temsirolimus and everolimus), advanced pancreatic neuroendocrine tumors (everolimus), and subependymal giant cell astrocytoma associated with tuberous sclerosis (everolimus). However, resistance to single-agent rapalog therapy occurs and may be related to either incomplete inhibition of the targeted pathway (such as phosphorylation of 4E-BP1 as discussed above) or loss of S6K-mediated feedback inhibition of growth factor receptor signaling leading to paradoxic hyperactive signaling. The normal feedback loop involves activated S6K, which phosphorylates and inactivates insulin receptor substrate-1 and inhibits signaling through the phosphoinositide 3-kinase (PI3K) pathway.[5, 9] In the presence of rapalogs, the feedback loop is abrogated, leading to continued PI3K signaling, TORC2 activation, and subsequent phosphorylation of AKT at Threonine 308 (T308) and Serine 473 (S473), which markedly enhances the activity of AKT.[2, 5, 9]

The loss of feedback inhibition by rapalogs has been demonstrated in clinical trials. In an analysis of either paired fresh tumor samples or skin biopsies obtained from 55 patients who received different doses of everolimus either daily or weekly in a phase 1 trial, everolimus inhibited TORC1 in a dose- and schedule-dependent manner with near complete inhibition of S6K.[10] Half the paired tumor samples had a posttreatment increase in the phosphorylation of AKT at S473.[10] These results provide direct evidence that loss of S6K feedback and subsequent PI3K/TORC2-induced activation of AKT occurs commonly in patients with solid tumors receiving single-agent everolimus.

MLN0128 is a potent, highly selective, ATP-competitive inhibitor of mTOR. MLN0128 is mechanistically distinct from the allosteric inhibitors of mTOR (rapamycin and its derivatives, referred to as rapalogs). The rapalogs only partially inhibit TORC1, whereas MLN0128 inhibits both TORC1 (more completely S6K and 4E-BP1) and TORC2. Dual TORC1/2 inhibition mitigates feedback activation of PI3K and AKT, known to cause resistance to TORC1-only inhibitors.[11]

1.2 Nonclinical Experience

MLN0128 inhibited the human ether-à-go-go related gene (hERG) potassium ion channel with a concentration producing 50% inhibition (IC_{50}) of approximately 175 µM. Given an in vitro mTOR kinase IC_{50} of 1.1 nM, MLN0128 it is not expected to have an effect on the

hERG channel at efficacious exposures in humans. Additionally, a Good Laboratory Practice (GLP)-compliant cardiovascular safety study in telemeterized monkeys demonstrated no effects on the body temperature, blood pressure, heart rate, or electrocardiogram (ECG) endpoints. There were also no effects on cardiovascular or respiratory parameters with MLN0128 in GLP-compliant toxicology studies. In the GLP-compliant, single-agent study of MLN0128 in Sprague-Dawley rats, gait effects were observed on Day 28; however, no similar effects have been observed in humans.

The toxicity profile of MLN0128 in rats and monkeys, as established in GLP-compliant repeat-dose studies, is consistent with pharmacologic inhibition of mTORC1/2 activity. The dose limiting toxicities (DLTs) of MLN0128 in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included gastrointestinal (GI) distress and decreased activity, appetite, and body temperature. Additional findings in rat and monkey repeat-dose toxicology studies with MLN0128 included bone marrow and lymphoid depletion, GI and skin effects, and effects on glucose and insulin levels, all of which can be monitored in clinical trials. The toxicities seen in the repeat-dose toxicology studies, such as GI effects and glucose and insulin increases, are consistent with the treatment-emergent adverse events (TEAEs), including mucositis and hyperglycemia, which have been observed to date in patients receiving MLN0128.

MLN0128 was negative in the Ames assay, in vivo comet assay, and in vivo micronucleus assay. An in vitro chromosomal aberration assay was positive. Thus, current evidence supports a low risk for genotoxicity for MLN0128.

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled MLN0128 suggest that MLN0128 is metabolized primarily via CYP1A2 (approximately 31% to 40%), with a minor contribution from CYP3A4 (approximately 11% to 22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyltransferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism.

In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with

MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Section 14.4) should only be administered with caution and at the discretion of the investigator during the study. Alternative treatments, if available, should be considered.

MLN0128 exhibits an inverse pH dependent aqueous solubility, having low solubility at high pH. pH modifying agents such as proton pump inhibitors (PPIs), H_2-receptor antagonists, or neutralizing antacids that can increase stomach pH can reduce MLN0128 absorption. In this study PPIs are not permitted; however, restricted use of H_2-receptor antagonists and neutralizing antacids is permitted (refer to Section 6.5 and Section 6.6).

Detailed information regarding the nonclinical pharmacology and toxicology of MLN0128 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

Single-agent MLN0128 is in clinical development with 2 phase 1 studies: a study in patients with advanced solid malignancies (INK128-001) and a study in patients with relapsed or refractory multiple myeloma or Waldenstrom macroglobulinemia (INK128-002). A third phase 1 study of MLN0128 is in combination with paclitaxel with or without trastuzumab in patients with advanced solid tumors (INK128-003). These studies have been designed to investigate the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of MLN0128 for the treatment of advanced solid tumors and hematologic malignancies either as a single agent or in combination with chemotherapy and/or human epidermal growth factor receptor 2 (HER2)-targeting agents. A phase 1b/2 study of MLN0128 in combination with exemestane or fulvestrant therapy in women with estrogen receptor positive (ER+)/HER2 negative (HER2–) advanced or metastatic breast cancer (Study C31001) is enrolling patients. Additionally, the combination of MLN0128 with MLN1117 (an oral PI3Kα inhibitor) is being evaluated in a phase 1b study in adult patients with advanced nonhematologic malignancies (Study C32001).

Further details on these studies are provided in the IB.

1.4 Study Rationale

MLN0128 is currently in phase 1 clinical investigation. In May 2012, the US FDA recommended that the effect of MLN0128 on rate-corrected QT interval (millisec) of electrocardiograph (QTc) be investigated before initiating phase 3 studies.

Assessment of the potential of an investigational agent to cause QTc prolongation as a biomarker for ventricular tachycardia is an essential component of new drug development, as drugs that prolong the QTc interval pose an increased risk for ventricular tachycardia and sudden cardiac death. While ECG data are collected during early clinical studies, often these data are not sufficient to provide a high degree of confidence in evaluation of the potential of a study drug to prolong the QT interval. Dedicated QTc studies are advantageous because extensive ECG data is collected prior to and immediately following dosing of the investigational agent. ECG measurements can be made to coincide with clinically relevant maximal concentrations of the investigational agent to provide a more robust assessment of the effect of the investigation agent on QTc interval.

The primary objective of this dedicated QT study is to characterize the effect of a single dose of 40 mg MLN0128 on the QTc interval in patients with advanced solid tumors. Two doses and schedules of MLN0128 are currently being investigated: 5 mg every day (QD) and 40 mg QW. The 40 mg QW is currently the highest dose of MLN0128 under clinical investigation. The 40 mg dose of MLN0128 is also the single agent maximum tolerated dose (MTD) of MLN0128 in the QW dosing schedule. MLN0128 does not accumulate in plasma to any meaningful extent with QD dosing and the maximum plasma concentration of MLN0128 with 5 mg QD dosing is unlikely to exceed those expected at the 40 mg QW dose of MLN0128. The 40 mg dose of MLN0128 will allow for the assessment of the effect of MLN0128 on QTc interval at its highest anticipated plasma concentration.

Since this study will be conducted in patients with advanced solid tumors, the study does not include placebo or a positive control (ie, moxifloxacin). In addition, since the 40 mg dose of MLN0128 represents its single agent MTD in the QW dosing schedule and is the highest dose of MLN0128 administered in clinical studies, the design of this dedicated QT study does not include a supratherapeutic dose of MLN0128. The collection of serial time-matched baseline ECGs should account for circadian changes, within patient inter-occasion variability in ECGs, and the determination of individual baseline corrected QTc (QTcI). ECGs will be collected in triplicate to further minimize variability. Time-matched collection of serial PK data of MLN0128 for concentration-QTc analysis will enable the understanding of changes in QTc with plasma concentration and projection of the effect of MLN0128 on QTc at doses that were not evaluated in this study.

MLN0128 is known to induce nausea and vomiting at the 40 mg dose. To mitigate this effect, patients will receive an antiemetic agent (0.25 mg palonosetron) before receiving the single dose of MLN0128. No significant effect of palonosetron on QT interval has been

observed at doses up to 2.25 mg in a thorough QT assessment;[12] thus, no effect on QT interval is anticipated with the prophylactic use of palonosetron during this study.

1.5 Potential Risks and Benefits

The most common TEAEs observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, and blood creatinine increased. In general, toxicities observed to date have been mostly Grade 1 or Grade 2 and are manageable with supportive care and/or dose interruption or dose reduction of MLN0128.

Risk mitigation strategies for potential adverse events (AEs) include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of AEs and serious adverse events (SAEs) by the sponsor. Refer to Section 6.8 for additional information.

The benefits of MLN0128 are discussed in Section 1.1.

Further details are presented in the MLN0128 IB.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is:

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

2.2 Secondary Objectives

The secondary objectives are:

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

3. STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is:

- Change in QTcI from time-matched baseline (Screening; Day -1) to Cycle 1, Day 1

3.2 Secondary Endpoints

The secondary endpoints are:

- AEs, SAEs, assessments of clinical laboratory values, and vital sign measurements
- Change from time-matched baseline (Screening; Day -1) in QTc with Bazett correction (QTcB), QTc with Fridericia correction (QTcF), QRS, PR, and heart rate on Cycle 1, Day 1
- PK parameters, including, but not limited to, single-dose maximum (peak) concentration (C_{max}), single-dose first time of occurrence of maximum (peak) concentration (T_{max}), area under the plasma concentration versus time curve from zero to the last measurable concentration (AUC_t), area under the plasma concentration versus time curve from zero to infinity (AUC_{inf}), and terminal disposition half-life ($t_{1/2}$)

4. STUDY DESIGN

4.1 Overview of 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/QTc interval in patients with advanced solid tumors.

The study will enable collection of time-matched PK and ECG data before and after MLN0128 administration at the time points specified in the Schedule of Events. A central ECG reader will be used and continuous 12-lead digital ECGs will be obtained using a Holter H12+ ECG recorder. All planned 12-lead ECG collections will be obtained in triplicate.

On the morning of Screening; Day -1 baseline measurements of serial triplicate ECGs (0-10 hours) will be obtained. Three Holter ECGs will be extracted at the time points matching the Cycle 1, Day 1 PK/ECG sampling times. As the Screening; Day -1 baseline evaluations serve as the time-matched baseline for the corresponding Cycle 1, Day 1 PK/ECG assessments, the 0-hour time point on Screening; Day -1 should coincide with the clock time of MLN0128 dosing on Cycle 1, Day 1 (the 0-hour time point on Cycle 1, Day 1). The clock time of all other ECG assessments on Screening; Day -1 should also coincide with the clock time of PK/ECG assessments for Cycle 1, Day 1. After collection of the planned 10-hour ECG sample on Cycle 1, Day 1, the Holter recorders will not be removed and patients will be furloughed from the study site.

On Screening; Day -1 and Cycle 1, Day 1, patients will be given the option to report to the site fasted or after having a light morning meal as long as the meal has been completed at least 2 hours before the scheduled baseline triplicate ECG on each day. If patients report to the site fasted, they should do so with adequate time (approximately 3 hours before the scheduled baseline triplicate ECG) in order to eat standard, light breakfast provided by the site that must be completed at least 2 hours before the scheduled baseline triplicate ECG on each day. Patients will be instructed not to eat for the next 6 hours (ie, 2 hours before the 0-hour, predose time point and until completion of the collection of the 4-hour postdose PK/ECG assessments). A standard, light lunch will be provided. Light meals will be administered at the same times on Screening; Day -1 and Cycle 1, Day 1.

For the Screening; Day -1 and Cycle 1, Day 1 study visits, fasting serum glucose will be measured at the clinical facility. In addition, all patients will be issued a glucometer and trained to use it to monitor their daily predose fasting blood glucose (FBG) levels at home for the days on which glucose is not measured at the clinic. Patients will be instructed to notify the study staff immediately with any abnormal readings (ie, ≥ 150 mg/dL) for further instructions on the management of hyperglycemia. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

To mitigate nausea and vomiting known to occur at a 40 mg dose of MLN0128, patients will be administered an antiemetic agent (0.25 mg palonosetron) on Cycle 1, Day 1.

After collection of the 10-hour postdose PK/ECG assessment on Cycle 1, Day 1, patients will be furloughed from the study site. The Holter recorders will not be removed during this furlough period.

On Cycle 1, Day 2 and Cycle 1, Day 3, patients may eat and drink up to approximately 2 hours before arriving at the study site for PK/ECG evaluations.

On Cycle 1, Day 2, patients will report to the clinical facility at least 1 hour before the 24-hour postdose PK/ECG (triplicate) assessments. After the PK/ECG assessments are completed, the Holter recorders will be removed and patients will be furloughed from the study site.

On Cycle 1, Day 3, patients will report to the clinical facility at least 1 hour before the 48-hour postdose assessments, which will represent the final study endpoint-specific planned PK/ECG assessments.

Patients may continue to receive MLN0128 if, in the opinion of the investigator, the patients are deriving clinical benefit, until they experience disease progression. Patients continuing treatment with MLN0128 at the discretion of the investigator will receive a dose of MLN0128 up to 30 mg QW. Dose escalation will not be permitted, and a maximum of 2 dose reductions (for patients experiencing study drug-related toxicity) will be permitted. Patients will return to the study site for follow-up visits at the time points in the Schedule of Events. Treatment may continue until disease progression, unacceptable MLN0128-related toxicity, withdrawal of consent, or for up to 12 months (whichever occurs first).

All patients enrolled in the study will attend the End-of-Study (EOS)/Early Termination visit 30 (to 40) days after receiving their last dose of study drug.

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.[13] DLTs are defined in Section 6.3.

AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of MLN0128.

Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) will be obtained at baseline and Cycle 3, Day 28, after which point CT (with contrast) or MRI may be performed every 3 cycles at the investigator's discretion as clinically indicated, according to standard of care.

4.2 Number of Patients

Approximately 30 patients will be enrolled in this study. Patients will be enrolled from approximately 6 study centers in the US. Enrollment is defined as the time of the initiation of the first dose of study drug.

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

4.3 Duration of Study

Patients may receive MLN0128 until they experience disease progression. Patients will discontinue treatment if they have an unacceptable MLN0128-related toxicity. The maximum duration of treatment will be 12 months unless, after discussion between the investigator and sponsor, it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Patients will attend an EOS/Early Termination visit 30 (to 40) days after receiving their last dose of study drug to permit the detection of any delayed treatment-related AEs.

It is anticipated that this study will last for approximately 12 months.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Men or women patients 18 years or older.

2. Patients must have a radiographically or clinically evaluable solid tumor for which standard-of-care therapy has failed; however, measurable disease as defined by modified Response Evaluation Criteria in Solid Tumors criteria (Version 1.1)[(14)] is not required for participation in this study.

3. Patients with a history of brain metastasis may be eligible for the study provided all of the following criteria are met:

    - Brain metastases which has been treated

- No evidence of disease progression or hemorrhage after treatment
- Off-treatment with dexamethasone for 28 days before administration of the first dose of MLN0128
- No ongoing requirement for dexamethasone or anti-epileptic drugs

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Section 14.1).

5. Female patients who:
   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 3 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 3 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7. Clinical laboratory values as specified below within 28 days before the first dose of study drug:

   - Total bilirubin must be ≤ 1.5 × the upper limit of normal (ULN)
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × the ULN. ALT and AST may be ≥ 5 × the ULN if the elevation can be reasonably ascribed to the presence of metastatic disease in liver.
   - Creatinine clearance ≥ 50 mL/min based either on Cockroft Gault estimate or based on a 12- or 24-hour urine collection. (refer to Section 14.3)
   - Absolute neutrophil count ≥ 1.5 × 10^9/L; platelet count ≥ 100 × 10^9/L; hemoglobin ≥ 10 g/dL
   - Fasting glucose ≤ 120 mg/dL and fasting triglycerides ≤ 300 mg/dL

8. Left ventricular ejection fraction (LVEF) within 5 absolute percentage points of institutional standard of normal, as measured by echocardiogram or multiple gated acquisition (MUGA) scan, within 28 days before the first dose of study drug (ie, if the institutional normal is 50%, LVEF may be as low as 45% to be eligible).

9. Ability to swallow oral medications, willingness to perform mucositis prophylaxis, and suitable venous access for the study-required blood sampling.

10. Patients requiring chronic treatment with H_2-receptor antagonists or neutralizing antacids are eligible; however, the most recent dose must have been more than 48 hours with H_2-receptor antagonists and more than 4 hours with neutralizing antacids before receiving the first dose of MLN0128. Treatment with H_2-receptor antagonists or neutralizing antacids is permitted after completing the required PK/ECG assessments on Cycle 1, Day 3 within the specified windows (refer to Section 6.6).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period.

2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3. Treatment with any investigational products within 14 days before the first dose of study drug and systemic anticancer therapy within 28 days before the first dose of study drug

4. Untreated brain metastasis or history of leptomeningeal disease or spinal cord compression.

5. Tumors with involvement of the mediastinum.

6. Failure to recover from the reversible effects of prior anticancer therapies with the exception of alopecia, and after-effects associated with prior tyrosine kinase inhibitor therapy such as hair depigmentation, hypothyroidism, and/or splinter hemorrhage.

7. Systemic corticosteroid (inhalers are allowed) within 7 days before the first dose of study drug.

8. Manifestations of malabsorption due to prior GI surgery, GI disease, or for an unknown or other reason that may alter the absorption of MLN0128.

9. Diagnosis of diabetes mellitus; patients with a history of transient glucose intolerance due to corticosteroid administration may be enrolled if all other inclusion/exclusion criteria are met.

10. History of any of the following within 6 months before study entry:

    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures

    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures

    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia)

    - Placement of a pacemaker for control of rhythm

- New York Heart Association Class III or IV heart failure
- Pulmonary embolism

11. Significant active cardiovascular or pulmonary disease at study entry, including:
    - Uncontrolled high blood pressure (ie, systolic blood pressure > 180 mmHg, diastolic blood pressure > 95 mmHg)
    - Resting pulse rate of < 50 beats per minute or > 100 beats per minute at screening or predose
    - Pulmonary hypertension
    - Uncontrolled asthma or O_2 saturation < 90% by arterial blood gas analysis or pulse oximetry on room air
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
    - Medically significant (symptomatic) bradycardia
    - History of arrhythmia requiring an implantable cardiac defibrillator
12. Requirement for QT-prolonging drugs with a risk of causing torsades de pointes (TdP). Patients on a stable dose of drugs with a conditional or possible risk of QT prolongation may be considered.
13. Baseline prolongation of QTc (eg, repeated demonstration of QTcF > 430 ms for men and QTcF > 450 ms for women, or TdP); other abnormal ECG findings deemed clinically significant by the investigator or which would interfere with determination of the QT interval, such as bundle branch block, abnormal T waves or pathological U waves.
14. History of thoracic surgery, Brugada syndrome, history of congenital long QT syndrome (LQTS; or family history of LQTS), or major surgery within 14 days before the first dose of study drug

15. Clinically significant comorbidities such as uncontrolled pulmonary disease, active central nervous system disease, active infection, serious infection within 14 days before the first dose of study drug, or any other condition that could compromise study participation by the patient.

16. Patients requiring daily or chronic use of PPI and/or having taken a PPI within 7 days before receiving the first dose of study drug.

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

MLN0128 is administered once weekly (QW) in continuous cycles of 28 days. MLN0128 will be supplied as capsules of 5 mg dose strength. All capsules will be swallowed whole. It is recommended that each dose of MLN0128 be given orally with 8 ounces (240 mL) of water.

Cycle 1, Day 1

During Holter ECG monitoring (Screening; Day -1 and Cycle 1, Day 1), patients will be given the option to report to the site fasted or after having a light morning meal, as long as the meal has been completed at least 2 hours before the scheduled baseline triplicate ECG on each day. If patients report to the site fasted, they should do so with adequate time (approximately 3 hours before the scheduled baseline triplicate ECG) to eat a light, standard breakfast provided by the site that will need to be completed at least 2 hours before the scheduled baseline triplicate ECG on each day. Patients will be instructed not to eat for the next 6 hours (ie, 2 hours before the 0-hour, predose time point and until completion of the collection of the 4-hour postdose PK/ECG assessments). A light, standard lunch will be provided at the same times on Screening; Day -1 and Cycle 1, Day 1.

On Cycle 1, Day 2 and Cycle 1, Day 3, patients may eat and drink up to approximately 2 hours before arriving at the study site for PK/ECG evaluations.

Patients will be required to swallow 8, 5mg capsules for a total dose of 40 mg MLN0128 on Cycle 1, Day 1. To mitigate nausea and vomiting known to occur at a 40 mg dose of MLN0128, patients will be administered an antiemetic agent (0.25 mg palonosetron), on

Cycle 1, Day 1, as an intravenous infusion over 30 seconds, at least 30 minutes before study drug administration.

Palonosetron is a commercially available drug; instructions are provided in the manufacturer's package insert.[12]

After Cycle 1, Day 3

After completing the required PK/ECG assessment period (Cycle 1, Day 3), patients may continue treatment with MLN0128 at the discretion of the investigator at a dose of MLN0128 30 mg QW. If patients experience severe emesis or mucositis preventing them from taking an MLN0128 dose, that dose will be skipped. If emesis occurs after study medication ingestion and whole capsule(s) are visible in the vomitus, replacement capsule(s) should be taken; otherwise the dose will not be re-administered, and patients should adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Patients should record the time of the emesis in their dosing diary cards (see the Study Manual). Under no circumstance should a patient repeat a dose or double-up doses. Patients should be instructed to take their study medication at approximately the same time each week and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. In the event, that, a patient fails to take the MLN0128 dose within the time frame specified (± 12 hours), that dose should be skipped. Patients should record any skipped doses in their dosing diary cards (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

Starting at Cycle 1, Day 8, patients are advised to take their doses of study drug with a light meal.

6.2 Reference/Control Therapy

No reference or placebo treatment will be used in this study. All patients will receive treatment with MLN0128.

6.3 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010.[13] These criteria are provided in the Study Manual. DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with MLN0128:

- Grade 3 or higher nonhematologic toxicity, despite adequate treatment, except for the following:
    - Grade 3 hyperglycemia lasting ≤ 14 days (all patients should receive optimal antiglycemic treatment, including insulin).
    - Grade 3 rash lasting ≤ 3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
- Grade 4 neutropenia lasting > 7 days in the absence of growth factor support.
- Grade 4 neutropenia of any duration accompanied by fever ≥ 38.5°C and/or systemic infection.
- Any other ≥ Grade 4 hematologic toxicity.
- Inability to administer at least 75% of planned doses of study drug within Cycle 1 due to treatment-related toxicity or delay in the initiation of the subsequent cycle of therapy by more than 14 days due to treatment-related toxicity (lack of adequate recovery of treatment-related hematological or nonhematological toxicities).
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk.

6.4 Dose-Modification Guidelines

MLN0128 is administered QW in continuous cycles of 28 days. Study drug should be administered continuously unless a ≥ Grade 3 MLN0128-related event occurs.

For management of toxicity for individual patients, dose adjustments may include interruption of treatment with study drug and a dose reduction. If continued treatment with MLN0128 is thought to be beneficial by the investigator, and with the sponsor's approval, dose reductions should be based on the guidelines provided below and in Table 6-1. Patients whose dose is reduced will not be allowed to re-escalate.

Dosing should be interrupted for ≥ Grade 3 MLN0128-related toxicities. If the event resolves to Grade 1 or baseline values within 14 days of interrupting treatment, depending on the severity of the toxicities, the patient may resume study drug as follows:

- Resume study treatment at 30 mg QW dose, or

- Resume study treatment at 20 mg QW (33% reduction)

If the toxicity recurs at the 20 mg QW dose, dosing should be interrupted. If the event resolves to Grade 1 or baseline values within 14 days of interrupting treatment, depending on the severity of the toxicity, the patient may resume study drug as follows:

- Resume study treatment at 20 mg QW, or
- Resume study treatment at 15 mg QW (25% dose reduction)

The sponsor's project clinician should be contacted before any dose modification of MLN0128 for any patient in the study.

Table 6-1 Dose Reduction Schedule for MLN0128

Dose Level	Percent Reduction	Dose
0	0%	30 mg QW
-1	33%	20 mg QW
-2	25%	15 mg QW

Abbreviation: QW = once weekly.

6.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

MLN0128 is administered in continuous cycles; therefore, study drug should be administered continuously unless a ≥ Grade 3 MLN0128-related event occurs. Patients who experience an AE meeting the definition for a DLT after Cycle 1, Day 3 should have their study drug treatment interrupted and reduced as outlined in Section 6.4.

6.4.2 Criteria for Dose Interruption During a Cycle

See Section 6.4 for dose modification guidelines.

6.4.3 Criteria for Dose Reduction

See Section 6.4 for dose modification guidelines.

6.4.4 Criteria for Discontinuation

Grade 4 nonhematologic toxicities will in general require that treatment with MLN0128 be permanently discontinued. If, in the opinion of the investigator and the project clinician, it is in the best interest of the patient to continue treatment with MLN0128, then the dose of

MLN0128 should be reduced by at least 1 dose level after recovery of the toxicity and/or intolerability to Grade 1 or to baseline values.

If dosing is delayed for > 14 consecutive days for MLN0128-related toxicities despite supportive treatment per standard clinical practice, or more than 2 dose reductions of MLN0128 are required for a patient, treatment should be stopped, the patient discontinued from the study, and the follow-up visit completed within 30 days of the last dose of MLN0128.

6.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- During the required PK/ECG assessment period (Cycle 1, Day 3), QT-prolonging drugs with a risk of causing TdP are prohibited. Patients on a stable dose of drugs with a conditional or possible risk of QT prolongation may be considered. (see Section 14.5).
- Radiation therapy for disease under study.
- Any investigational agent other than MLN0128 or mTOR inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for pre-existing lesions).
- Systemic corticosteroids (either intravenous [IV] or oral steroids, excluding inhalers), unless necessary for treatment of an MLN0128-related AE (eg, rash).
- Anti-epileptic drugs for patients with a history of treated brain metastasis.
- Anti-emetic agents (eg, 5-HT3 receptor antagonists) associated with a risk for QT prolongation, including ondansetron and granisetron. After completing the required PK/ECG assessment period (Cycle 1, Day 3), treatment with granisetron is permitted according to standard of care.
- PPIs; examples of PPIs include: omeprazole, esomeprazole, lansoprazole, and pantoprazole.

- Strong cytochrome P450 (CYP) 1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator. Refer to Section 14.4 for a list of these agents. Alternative treatments, if available, should be considered.

6.6 Permitted Concomitant Medications and Procedures

Restricted use of H_2-receptor antagonists or neutralizing antacids is permitted after completion of the required PK/ECG assessments on Cycle 1, Day 3, for patients continuing to receive treatment with MLN0128, under the following conditions:

- Treatment with H_2-receptor antagonist is not permitted less than 24 hours before and within 6 hours after receiving a dose of MLN0128. Examples of H_2-receptor antagonist include: ranitidine, cimetidine, and nizatidine.

- Treatment with neutralizing antacids is not permitted less than 4 hours before and within 6 hours after receiving a dose of MLN0128.

Other medications considered necessary for the safety and well-being of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the electronic case report form (eCRF).

6.7 Precautions and Restrictions

Dietary restrictions include periods of fasting as described in Section 7.4.16, and in-home daily fasting glucose monitoring (refer to Section 7.4.18).

Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low-carbohydrate diet.

It is not known what effects MLN0128 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 3 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 3 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.8 Management of Clinical Events

6.8.1 Management of Nausea and/or Vomiting

This study will employ prophylactic anti-emetic on Cycle 1, Day 1.

For patients remaining in the study after completing the required PK/ECG assessment period (Cycle 1, Day 3), guidance for the management of nausea and/or vomiting is provided in Table 6-2.

Table 6-2 Management of Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; consider IV fluid hydration	None
≥ 3	Inadequate oral intake; ≥ 6 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; initiate tube feeding, IVF, or TPN	Hold until ≤ Grade 1; resume MLN0128 without dose modification
Prevention/Prophylaxis Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of MLN0128 as needed throughout the study.			

Abbreviations: IV = intravenous; IVF = intravenous fluids; TPN = total parenteral nutrition.

6.8.2 Management of Hyperglycemia

In addition to obtaining fasting glucose levels at the clinic visits as outlined in the Schedule of Events, all patients will be provided with a glucometer and trained to use it to monitor their daily predose FBG levels at home. Patients will be instructed to notify the study staff immediately of any abnormal readings (ie, ≥ 150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the FBG level are observed during a minimum of 6 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to twice weekly if the investigator approves. Patients will continue to notify the investigator of FBG levels ≥ 150 mg/dL, and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. Guidelines for management of hyperglycemia are presented in Table 6-3.

Table 6-3 Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	FBG > ULN–160 mg/dL	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	FBG > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥ 3	FBG > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume MLN0128 based on timing of recovery: • ≤ 1 week: resume at same dose and schedule • > 1 but ≤ 2 weeks: reduce by 20% • 2 weeks: stop MLN0128 and discontinue patient from the study
Prevention/Prophylaxis • Follow fasting glucose levels during clinic visits. • Monitor home glucometer test results. • Check HbA1c levels every 3 months during therapy. • Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity). • Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher grade hyperglycemia. • FBG levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.			

Abbreviations: FBG = fasting blood glucose; HbA1c = glycosylated hemoglobin; ULN = upper limit of the normal range.

If any fasting glucose reading performed at the site indicates hyperglycemia (fasting glucose > ULN or ≥ 110 mg/dL), the study staff should first confirm that the patient was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours before). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

Based on the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or Grade 2 and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia. All patients developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose > ULN ≤ 160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent, such

as metformin. All patients with ≥ Grade 2 hyperglycemia (fasting glucose > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128 treatment. The investigator should consult an endocrinologist if needed to aid in optimizing the hyperglycemia treatment plan of the patient.

It is recommended that patients be treated initially with a fast-acting insulin sensitizer, such as metformin at 500 mg orally QD, and titrate up to a maximum of 1000 mg orally twice daily as needed. Concurrent addition to metformin of dipeptidyl peptidase-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency.

6.8.3 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 6-4.

Table 6-4 Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Cholesterol: > ULN-300 mg/dL Triglycerides: > 150-300 mg/dL	None	None
2	Cholesterol: > 300-400 mg/dL Triglycerides: > 300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥ 500 mg/dL should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Cholesterol: > 400-500 mg/dL Triglycerides: > 500-1000 mg/dL	Same as for Grade 2	Hold dose until recovery to ≤ Grade 1, then restart with a 20% dose reduction.
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2	Discontinue treatment.

Prevention/Prophylaxis

- Lifestyle modifications, as appropriate (balanced diet, limited consumption of alcoholic beverages, increased physical activity).

Table 6-4 Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification

Abbreviation: ULN = upper limit of normal.

6.8.4 Management of Oral Mucositis

Guidance for the management of oral mucositis is provided in Table 6-5.

Table 6-5 Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms	Nonalcoholic mouth wash or 0.9% salt water rinse; consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain not interfering with oral intake; modified diet indicated	Topical analgesic mouth treatments; topical corticosteroids; initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Severe pain interfering with oral intake	Same as for Grade 2; consider intralesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart with a 20% dose reduction.
4	Life-threatening consequences	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue treatment.

Prevention/Prophylaxis

- Consider initiation of a nonalcoholic mouth wash or 0.9% salt water rinses 4-6 times daily with start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

6.8.5 Management of Rash

Guidance for management of rash is provided in Table 6-6.

Table 6-6 Management of Rash

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ ointment and/or oral antihistamines.	None
≥ 3	Macules/papules covering > 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ ointment, oral antihistamines, and/or pulsed steroids.	Hold until ≤ Grade 2; resume MLN0128 based on timing of recovery: ≤ 2 weeks: reduce dose by 20% > 2 weeks: stop MLN0128 and discontinue patient from the study

6.8.6 Blinding and Unblinding

This is an open-label study.

6.9 Description of Investigational Agents

MLN0128 will be supplied as capsules for oral administration. A dose strength containing 5 mg of MLN0128, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule, will be used in this study. The 5 mg dose strength is formulated into size 2 capsules and is a gray, opaque color.

Refer to the MLN0128 IB for full details.

Palonosetron is a commercially available drug.[12]

6.10 Preparation, Reconstitution, and Dispensation

MLN0128 study drug will be provided in 60-cc high-density polypropylene (HDPE) bottles with child-resistant caps and induction seal. Study drug will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 capsules.

6.11 Packaging and Labeling

MLN0128 study drug will be provided by Millennium and will be handled at the investigative site as open-label material. MLN0128 capsules are packaged in 60-cc HDPE bottles with child-resistant caps and induction seal. Each bottle contains 30 capsules and will have a label containing pertinent study information, country-specific requirements, and a caution statement.

6.12 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN0128 study drug should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 86°F). All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access. All MLN0128 should be used before the shelf-life date.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

Because MLN0128 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of MLN0128. Patients will also receive diary cards to record dosing compliance of MLN0128 and instructions for their completion.

Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

Please refer to the Study Manual for additional instructions.

Palonosetron should be stored according to instructions provided in the manufacturer's package insert.[12]

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium Study Monitor for this study, the local laboratory and any additional clinical laboratories and other third party vendors may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

This is a single-dose, open label study.

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent (IC) before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 7.4.10.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

7.4.5 Patient Height and Weight

Height will be measured only during screening only. Weight will be measured at the time points specified in the Schedule of Events.

7.4.6 Vital Signs

Vital sign measurements include supine (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature. When the timing of vital sign measurements coincides with the timing of a blood sample (eg, for PK), the vital sign measurements should be completed before the blood sample.

7.4.7 Pregnancy Test

A serum pregnancy test will be completed as specified in the Schedule of Events by all women of childbearing potential; this test must be negative for the patient to be enrolled. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

7.4.8 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status (refer to Section 14.1) will be assessed at the times specified in the Schedule of Events.

7.4.9 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan or ECHO will be administered at the time points specified in the Schedule of Events.

7.4.10 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF throughout the study as specified in the Schedule of Events. See Section 6.5 and Section 6.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

7.4.11 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 9 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.12 Enrollment

A patient is considered to be enrolled in the study when the first dose of MLN0128 is administered. Procedures for completion of the enrollment information are described in the Study Manual.

7.4.13 Electrocardiogram

There are 2 types of ECGs acquired in this study: single, 12-lead safety ECGs and triplicate, 12-lead Holter monitoring. All ECGs will be administered at the time points specified in the Schedule of Events.

7.4.13.1 Single, 12-Lead Safety Electrocardiograms

The first type of ECG acquired for this study consists of ECG tracings that are acquired using a standard 12-lead digital ECG machine. These tracings will be reviewed by the investigator or trained designee at the study center. The ECG printout of parameters including PR, QRS, QT, QTcB, and QTcF intervals is acceptable for purposes of safety before dosing. All machine-generated tracings should be acquired in the supine position after the patient has been resting for 5 minutes. These ECGs are not included in the final QT analysis of this study.

7.4.13.2 Serial, Triplicate, 12-Lead Holter Monitoring Electrocardiograms

The study ECGs that are included in the final statistical analysis will be acquired from the 12-lead continuous ECG (Holter) recorders using the H-12 Plus ambulatory electrocardiograph recorder (Mortara Instruments, Milwaukee, WI), with high-frequency flashcards at a sampling rate of 1000 samples per second.

On Screening; Day -1, Holter ECG monitoring (0-10 hours) will be performed for baseline measurements. Three serial triplicate ECGs will be extracted at prespecified time points at times that match the times of Cycle 1, Day 1 postdose PK/ECG sampling.

As the Screening; Day -1 baseline evaluations are intended to serve as a time-matched baseline for corresponding Cycle 1, Day 1 ECG evaluations, it is critical to ensure that the 0-hour time point on Screening; Day -1 is timed to coincide with the clock time of the time of dosing of MLN0128 on Cycle 1, Day 1 (which will be considered the 0-hour time point on Cycle 1, Day 1).

Before each nominal ECG time point, the patient must have been supine in bed for 5 minutes. The triplicate ECGs will be extracted at approximately 2- to 5-minute intervals over a10-minute period following the rest period (the ECG extraction 15-minute window, ending at the nominal time point). Blood samples for PK analysis will be obtained immediately following the completion of the ECG extractions.

Additionally, patients will undergo Holter ECG monitoring on Cycle 1, Day 1 as described on Cycle 1, Day 1, and triplicate ECGs will be extracted at the matched PK time points over the steady-state dosing interval to contribute to analysis of the effect of steady-state concentrations of MLN0128 on QT/QTc intervals.

The 12-lead ECGs are extracted in triplicate, free from artifact, wandering, and at a time that the heart rate has been stabilized. All QT intervals will be measured using representative beats in the superimposed 12-lead "global" display. The measurement of QT, RR, PR, and QRS intervals are initiated in the semi-automatic mode and then adjusted appropriately by cardiovascular physicians; thereby, they are visually validated or manually adjusted and diagnostic findings are determined. The cardiovascular physicians are assigned in a subject-specific manner.

7.4.14 Disease Assessment

For patients remaining in the study after completing the required PK/ECG assessment period (Cycle 1, Day 3), CT with contrast as appropriate, MRI, X-ray, and/or bone scanning may be performed at the investigator's discretion as clinically indicated, according to standard of care. Assessments will be performed at the time points specified in the Schedule of Events. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

7.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined below:

Clinical Chemistry, Hematology, and Urinalysis

Clinical chemistry, hematology, and urinalysis laboratory evaluations must be available and reviewed by the investigator before enrollment and initial administration of MLN0128.

Blood samples for analysis of the following clinical chemistry and hematological parameters, urine samples for urinalysis, and prospective monitoring for hyperlipidemia through fasting lipid testing will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium
- Glycosylated hemoglobin (HbA1c) – at the times specified in the Schedule of Events

Urinalysis

- Turbidity and Color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Occult Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

Fasting Lipid Profile

- Total cholesterol
- Triglycerides
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)

7.4.16 Requirements for Fasting Periods

On Screening; Day -1 and Cycle 1, Day 1, patients will be given the option to report to the site fasted or after having a light morning meal, as long as the meal has been completed at least 2 hours before the scheduled baseline triplicate ECG on each day. If patients report to the site fasted, they should do so with adequate time (approximately 3 hours before the scheduled baseline triplicate ECG) in order to eat standard, light breakfast provided by the site that must be completed at least 2 hours before the scheduled baseline triplicate ECG on each day. Patients will be instructed not to eat for the next 6 hours (ie, 2 hours before the 0-hour, predose time point and until completion of the collection of the 4-hour postdose PK/ECG assessments). A standard, light lunch will be provided. Light meals will be administered at the same times on Screening; Day -1 and Cycle 1, Day 1.

On Cycle 1, Day 2 and Cycle 1, Day 3, patients may eat and drink up to approximately 2 hours before arriving at the study site for PK/ECG evaluations; see Section 7.4.19 and Section 7.4.13.2.

Beginning with Cycle 1, Day 4, patients will be instructed to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for daily glucose monitoring; see Section 7.4.17 and Section 7.4.18. Starting with Cycle 1, Day 8, patients are advised to take their doses of study drug with a light meal.

7.4.17 Fasting Glucose

Fasting glucose will be measured at the time points specified in the Schedule of Events before administration of MLN0128. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for each of these measurements beginning on Cycle 1, Day 4; see Section 7.4.16.

7.4.18 In-Home Daily Fasting Glucose Monitoring

Patients will be instructed to complete daily glucose monitoring at home after fasting overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours) for each of these measurements beginning on Cycle 1, Day 4; see Section 7.4.16 for fasting requirements. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded into source documents. Based on investigator judgment and upon the 6 consecutive months of well-controlled blood glucose levels, the frequency of in-home fasting glucose testing may be reduced to twice weekly. During this period of reduced monitoring, patients will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL. If blood glucose levels are not well controlled at any time during the study, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, in-home testing of fasting blood glucose levels will be resumed daily with the provided glucometer. On study visit days where fasting glucose is assessed in the clinic, the in-home daily fasting glucose monitoring does not need to be completed.

7.4.19 Pharmacokinetic Measurements

During Cycle 1, serial blood samples for PK analysis of MLN0128 will be collected over a 3-day period (0-48 hours) at the time points specified in the Schedule of Events. The dates and exact times of administration of MLN0128 before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF.

There is no protocol-specified PK sampling after Cycle 1.

7.5 Completion of Treatment/Completion of Study

Patients will be considered to have completed the study if they discontinue from the study for any of the reasons outlined in Section 7.6.

7.6 Discontinuation of Treatment with Study Drug and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- Adverse event
- Protocol violation
- Progressive disease
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the EOS visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

If a patient is deemed not evaluable by the sponsor, the postdose Cycle 1, Day 1 Holter ECG monitoring and PK sampling procedures need not be performed, since the patient would need to be replaced for the purposes of the PK/QTc objective of the protocol.

Patients who are withdrawn from treatment before completing study-required PK/ECG assessments for reasons other than DLT will be replaced. The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

7.7 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients will receive a sufficient quantity of MLN0128 for each treatment cycle and a diary in which to record their dosing. The study center staff will check the patient's diary versus the patient's supply of remaining MLN0128 at each study visit to ensure proper compliance

with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock. Separate analysis plans will be developed for ECG data derived from the triplicate, 12-lead Holter monitoring and for PK/QTc modeling.

8.1.1 Determination of Sample Size

Based on historical data, the within-subject standard deviation in QTcF change from baseline is approximately 9 msec. A sample size of 30 evaluable patients will provide a half-width of a 2-sided 90% confidence interval for the mean change from baseline in QTcF of 2.7 msec.

8.1.2 Randomization and Stratification

No randomization is planned for this study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: patients who receive at least 1 dose of MLN0128 will be used for all safety analyses, as well as efficacy analyses.
- PK population: patients who receive at least 1 dose of MLN0128 and have sufficient concentration-time data to calculate one or more PK parameters.
- ECG population: patients who receive at least 1 dose of MLN0128 and have at least 1 post-baseline ECG on Cycle 1, Day 1 will be used for all analyses of ECGs.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Data that are potentially spurious

or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

Investigator assessment of response will be provided in a data listing.

8.1.7 Electrocardiogram Analysis

Determination of QTcI

The QTcI will be based on the slope (exponent) of the QT-RR relationship derived from the acquisition of QT intervals from a 24-hour Holter recording on Screening; Day -1 (baseline) for each patient. The patient-specific, individual correction is an improvement over the fixed formulas commonly deployed. The patient-specific slope will be calculated using all pairs of QT and RR interval data on Screening; Day -1 separately for each patient. The linear regression: log (QT) = log (a) + b*log (RR) will be used to calculate the individual slope (b) for each patient. The QTcI will be calculated as: $QTcI = QT/RR^b$.

Electrocardiogram Analysis

The primary analysis of ECG parameters from the 24-hour Holter recordings will be based on a repeated measures mixed effects linear model. Mean changes (adjusted) and 1-sided 95% upper confidence bounds in QTcI, QTcF, QTcB, and heart rate will be generated for each of the time-matched changes from baseline. Descriptive statistics for the actual values of ECG intervals (QTcI, QTcF, QTcB, PR interval, RR interval, QRS duration) and heart rate will be tabulated by scheduled time point.

The following categorical analyses of QTc intervals (QTcI and QTcF), PR interval, and QRS duration will be performed at each scheduled time point and on the maximum value for each patient:

- QTc interval > 450 msec
- QTc interval > 480 msec

- QTc interval > 500 msec
- QTc interval increases from baseline > 30 msec
- QTc interval increases from baseline > 60 msec
- QRS interval > 110 msec and 25% increase from baseline
- PR interval > 200 msec and 25% increase from baseline

New ECG morphologies, not present at Screening; Day -1 (baseline), will be summarized.

8.1.8 Pharmacokinetics

Pharmacokinetic Analysis

Individual and mean plasma concentration data will be plotted over time. Descriptive statistics will be presented for plasma PK parameters including, but not limited to, C_{max}, T_{max}, AUC_t, AUC_{inf}, and $t_{1/2}$. Individual and mean MLN0128 plasma concentration-time data will be plotted.

PK/QTc Analysis

The relationship between plasma MLN0128 concentration and effects on heart rate and QTcI/QTcF will be analyzed using nonlinear mixed effects modeling. It is expected that the relationship between plasma MLN0128 concentrations and change from time-matched baseline values of QTc will be described using a direct linear concentration-effect relationship; however, the selection of the final model and mathematical form of the concentration-effect relationship will be based on graphical assessment of the data (eg, visual examination of observed concentration-effect plots to rule out a hysteresis secondary to time-delayed effects on QTc) and exploration of alternate structural models (eg, maximum effect attributed to the drug [E_{max}] models). The final model will be used to predict the population average change in QTc and its corresponding 1-sided 95% upper confidence bounds in the mean steady-state C_{max} of MLN0128 after a single dose of 40 mg MLN0128. A separate PK/QTc analysis plan will be developed and the results of these PK/QTc modeling analyses will be reported separately.

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug-related TEAEs
- The most commonly reported TEAEs
- SAEs

A listing of TEAEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN0128 safety profile.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN0128.

8.1.10 Interim Analysis

Not applicable.

8.2 Pharmacokinetic Modeling

Refer to Section 8.1.8.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.1.2 Adverse Event Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

9.1.3 Serious Adverse Event Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[13] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to

function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell (WBC) count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

9.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 9.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 9.1) must be reported (see Section 9.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information
Cognizant
US and Canada
Fax: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious

pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[13] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

9.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.
- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 9.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10. ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

10.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

10.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

10.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

10.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

10.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

10.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

10.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call MedComm Solutions at 877-674-3784 (877 MPI DRUG) (US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed according to the procedures outlined in Section 9.2.

10.12 Closure of the Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the

event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

10.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

11. USE OF INFORMATION

All information regarding MLN0128 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN0128 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

12. INVESTIGATOR AGREEMENT

I have read Protocol C31002 Amendment 2: A Phase 1 Study to Evaluate the Effect of MLN0128 on the QTc Interval in Patients With Advanced Solid Tumors, I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

13. REFERENCES

1. Laplante M, Sabatini DM. mTOR Signaling. Cold Spring Harb Perspect Biol 2012;4(2).
2. Laplante M, Sabatini, DM. mTOR Signaling in Growth Control and Disease. Cell 2012;149(2):274-93.
3. Sabatini DM. mTOR and cancer: insights into a complex relationship. Nature Reviews. Cancer 2006;6(9):729-34.
4. Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. Nature Reviews. Drug Discovery 2011;10(11):868-80.
5. Vilar E, Perez-Garcia J, Tabernero J. Pushing the envelope in the mTOR pathway: the second generation of inhibitors. Molecular Cancer Therapeutics 2011;10(3):395-403.
6. Thoreen CC, Kang SA, Chang JW, Liu Q, Zhang J, Gao Y, et al. An ATP-competitive mammalian target of rapamycin inhibitor reveals rapamycin-resistant functions of mTORC1. Journal of Biological Chemistry 2009;284(12):8023-32.
7. Chresta CM, Davies BR, Hickson I, Harding T, Cosulich S, Critchlow SE, et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Research 2010;70(1):288-98.
8. Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulikakos PI, Scaltriti M, Moskatel E, et al. mTOR kinase inhibition causes feedback-dependent biphasic regulation of AKT signaling. Cancer Discov 2011;1(3):248-59.
9. O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, et al. mTOR Inhibition Induces Upstream Receptor Tyrosine Kinase Signaling and Activates Akt. Cancer Res 2006;66(3):1500-8.
10. Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008;26(10):1603-10.
11. De P, Sun Y, Wu H, Rommel C, Yi L, Dey N, et al. Pre-clinical potency of INK128, a highly potent TORC1/2 kinase inhibitor in the HER2 amplified breast cancer model. Cancer Research 2012;72(Abstract 2240).
12. ALOXI® (palonosetron HCl) injection for Intravenous Use [package insert]. Switzerland: Helsinn Healthcare SA; 2009.

13. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

16. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

14. APPENDICES

14.1 Eastern Cooperative Oncology Group Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[15]

14.2 New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[16]

14.3 Cockcroft-Gault Equation

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\frac{0.85\,(140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[17]

14.4 List of Relevant Cytochrome P_{450} Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
cimetidine	methoxsalen	
Strong CYP1A2 Inhibitors		
fluvoxamine	ciprofloxacin	
Clinically Significant Enzyme Inducers		
carbamazepine	rifabutin	St. John's wort
phenobarbital	rifampin	phenytoin
rifapentine		

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
Note that these lists are not exhaustive.

14.5 Exclusionary QT-Prolonging Drugs

The following table contains a list of QT-prolonging drugs according to the Arizona Center for Education and Research on Therapeutics. QT-prolonging drugs with a risk of causing torsades de pointes (TdP) are exclusionary in this study. Patients on a stable dose of drugs with a conditional or possible risk of QT prolongation or drugs that are to be avoided by patients with congenital long QT syndrome may be considered pending discussion and agreement with the project clinician.

Exclusionary QT-Prolonging Drugs

Drug Class	Risk of TdP[a] Name (Brand Name)	Conditional or Possible Risk of TdP[b] Name (Brand Name)	Congenital QTc Name (Brand Name)
Antianginal		ranolazine (Ranexa)	
Antiarrhythmic	amiodarone (Cordarone, Pacerone) bepridil (Vascor) disopyramide (Norpace) dofetilide (Tikosyn) flecainide (Tambocor) ibutilide (Corvert) procainamide (Pronestyl, Procan) quinidine (Cardioquin, Quinaglute) sotalol (Betapace)	dronedarone (Multaq)	
Antibiotic	azithromycin (Zithromax) clarithromycin (Biaxin) erythromycin (Erythrocin, EES) moxifloxacin (Avelox) pentamidine (NebuPent, Pentam) sparfloxacin (Zagam)	ciprofloxacin (Cipro) gatifloxacin (Tequin) gemifloxacin (Factive) levofloxacin (Levaquin) ofloxacin (Floxin) roxithromycin (Rulide) telithromycin (Ketek) trimethoprim-sulfa (Sulfa, Bactrim)	
Anticancer	arsenic trioxide (Trisenox) vandetanib (Caprelsaa)	Eribulin (Halaven) lapatinib (Tykerb, Tyverb) nilotinib (Tasigna) sunitinib (Sutent)	
Anticonvulsant/ Seizure		felbamate (Felbatrol) fosphenytoin (Cerebyx)	
Antidepressant	citalopram (Celexa)	amitriptyline (Elavil) clomipramine (Anafranil) desipramine (Pertofrane) doxepin (Sinequan) escitalopram (Lexapro, Cipralex) fluoxetine (Prozac, Sarafem) imipramine (Norfranil)	

Exclusionary QT-Prolonging Drugs

Drug Class	Risk of TdP[a] Name (Brand Name)	Conditional or Possible Risk of TdP[b] Name (Brand Name)	Congenital QTc Name (Brand Name)
		lithium (Eskalith, Lithobid) nortriptyline (Pamelor) paroxetine (Paxil) protriptyline (Vivactil) sertraline (Zoloft) trazodone (Desyrel) trimipramine (Surmontil) venlafaxine (Effexor)	
Antiemetic	domperidone (Motilium) droperidol (Inapsine)	dolasetron (Anzemet) granisetron (Kytril) ondansetron (Zofran) tamoxifene (Nolvadex)	
Antifungal		fluconazole (Diflucan) itraconazole (Sporanox) ketoconazole (Nizoral) voriconazole (Vfend)	
Antihistamine	astemizole (Hismanal) terfenadine (Seldane)	diphenhydramine (Benadryl, Nytol)	
Antihypertensive/ Diuretic		indapamide (Lozol) isradipine (Dynacirc) moexipril/HCTZ (Uniretic) nicardipine (Cardene)	
Antilipemic/ Hypercholesterolemia	probucol (Lorelco)		
Antimalarial	chloroquine (Aralen) halofantrine (Halfan)		
Antipsychotic	chlorpromazine (Thorazine) haloperidol (Haldol) mesoridazine (Serentil) pimozide (Orap) thioridazine (Mellaril)	amisulpride (Solian) clozapine (Clozaril) iloperidone (Fanapt) paliperidone (Invega) quetiapine (Seroquel)	

Exclusionary QT-Prolonging Drugs

Drug Class	Risk of TdP[a] Name (Brand Name)	Conditional or Possible Risk of TdP[b] Name (Brand Name)	Congenital QTc Name (Brand Name)
		risperidone (Risperdal) sertindole (Serdolect, Serlect) ziprasidone (Geodon)	
Antiviral/ HIV infection		foscarnet (Foscavir)	
Appetite suppressant/dieting, weight loss			fenfluramine (Pondimin) phentermine (Adipex, Fastin) sibutramine (Meridia)
Benign prostatic hyperplasia		alfuzosin (Uroxatral)	
ß2-receptor/asthma			albuterol (Proventil, Ventolin)
Bladder antispasmodic			Tolterodine (Detrol LA, Detrol)
Bronchodilator			ephedrine (Broncholate, Rynatuss) levalbuterol (Xopenex) metaproterenol (Alupent, Metaprel) terbutaline (Brethine)
Catecholamine			epinephrine (Bronkaid, Primatene) isoproterenol (Isupres, Medihaler-Iso) dobutamine (Dobutrex)
Cholinesterase inhibitor/ Dementia, Alzheimer's		galantamine (Reminyl)	
CNS stimulant/ADHD			amphetamine (Adderall, Dexedrine) dexmethylphenidate (Focalin) lisdexamfetamine (Vyvanse) methlphenidate (Concerta,

Exclusionary QT-Prolonging Drugs

Drug Class	Risk of TdP[a] Name (Brand Name)	Conditional or Possible Risk of TdP[b] Name (Brand Name)	Congenital QTc Name (Brand Name)
			Ritalin)
Decongestant/allergies, sinusitis, asthma			Phenylpropanolamine (Acutrim, Dexatrim) pseudoephedrine (PediaCare, Sudafed)
Dopaminergic		amantadine (Symmetrel)	
Endocrine		octreotide (Sandostatin)	
Erectile dysfunction		vardenafil (Levitra)	
GI stimulant/Heartburn	cisapride (Propulsid)		
Imaging contrast agent/ Echocardiography		perflutren lipid microspheres (Definity)	
Immunosuppressant		fingolimod (Gilenya) tacrolimus (Prograf)	
Inotropic agent/heart failure, hypotension, shock			dopamine (Intropine)
Local anesthetic			cocaine (Cocaine)
Muscarinic receptor anatagonist/ overactive bladder		solifenacin (VESIcare)	
Muscle relaxant		tizanidine (Zanaflex)	
Norepinephrine reuptake inhibitor/ADHD			atomoxetine (Strattera)
Opiate agonist	levomethadyl (Orlaam) methadone (Dolophine, Methadose)		
Oxytocic		oxytocin (Pitocin)	
Peptic ulcer/GERD/ H_2-receptor antagonist		famotidine (Pepcid)	

Exclusionary QT-Prolonging Drugs

Drug Class	Risk of TdP[a] Name (Brand Name)	Conditional or Possible Risk of TdP[b] Name (Brand Name)	Congenital QTc Name (Brand Name)
Protease inhibitor/HIV		atazanavir (Reyataz) ritonavir (Norvir)	
Sedative		chloral hydrate (Noctec)	
Sympathomimetic/asthma/ COPD			salmeterol (Serevent)
Uterine relaxant/prevent premature labor			ritodrine (Yutopar)
Vasoconstrictor, inotrope/shock, low blood pressure			norepinephrine (Levophed)
Vasoconstrictor, decongestant/ low blood pressure			phenylephrine (Neo-Synephrine) midodrine (ProAmatine)

Source: Based on Woosley RL. Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes. Arizona Center for Education and Research on Therapeutics. azcert.org/medical-pros/drug-lists/printable-drug-list.cfm. Last revised 24 June 2012.

Abbreviations: ADHD = Attention deficit hyperactivity disorder; COPD = chronic obstructive pulmonary disorder; CNS = central nervous system; EES = erythromycin ethylsuccinate; GERD = gastroesophageal reflux disease; TdP = Torsades de Pointes.

Exclusions applicable only to listed drugs. Names in parenthesis are United States trade names. Drugs often have more than one brand name. For this table, only the 2 most common brand names are included.

a Drugs that are generally accepted by authorities to have a risk of causing TdP.

b Drugs that may prolong the QT interval but at this time lack substantial evidence for causing TdP.

c Drugs to be avoided, if possible, by patients with Congenital Long QT Syndrome.

14.6 Amendment 2 Detailed Summary of Changes

The primary section(s) of the protocol affected by the changes in Amendment 2 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.

The primary change occurs in Section 5.2 Exclusion Criteria:

Deleted text: ~~16. Patients requiring treatment with strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9. Treatment with strong CYP3A4 and CYP2C19 inducers and/or inhibitors must be discontinued at least 14 days before the first dose of study drug. Treatment with moderate inhibitors of CYP2C9 must be discontinued at least 7 days before the first dose of study drug.~~

Rationale for Change:

This change, which removes enrollment restrictions for patients taking CYP3A4, CYP2C9, or CYP2C19 inhibitors and/or inducers in this study, was made to allow more flexibility in patient enrollment based on updated data on MLN0128 metabolism by specific CYP isoforms.

Change 2: Update the list of concomitant medications prohibited during the study.

The primary change occurs in Section 6.5 Excluded Concomitant Medications and Procedures:

Previous text: Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2CP. After completing the required PK/ECG assessment period (Cycle 1, Day 3), treatment with 1 or more of the strong CYP3A4 or CYP2C19 inhibitors and/or inducers and moderate inhibitors of CYP2CP may be considered after consultation with the project clinician. A list of strong inhibitors and strong inducers of CYP2C9, CYP2C19, and CYP3A4 is included in Section 14.4.

Amended or new wording:	Strong **cytochrome P450 (CYP) 1A2 inhibitors and CYP** ~~CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2CP. After completing the required PK/ECG assessment period (Cycle 1, Day 3),~~ inducers **should be administered with caution and at the discretion of the investigator. See** ~~treatment with 1 or more of the strong CYP3A4 or CYP2C19 inhibitors and/or inducers and moderate inhibitors of CYP2CP may be considered after consultation with the project clinician. A list of strong inhibitors and strong inducers of CYP2C9, CYP2C19, and CYP3A4 is included in~~**. Refer to** Section 14.4 **for a list of these agents**. **Alternative treatments, if available, should be considered.**

Rationale for Change:

This change was made to update the recommendations on concomitant medication use during the study based on MLN0128 metabolism by specific CYP isoforms

Change 3: Update the description of potential drug-drug interactions.

The primary change occurs in Section 1.2 Nonclinical Experience

Initial wording:	In-vitro, MLN0128 is metabolized by various cytochrome P450 (CYP) enzymes, including 2C19 (35%), 3A4 (28%), and 2C9 (28%); MLN0128 neither inhibited nor induced any of the major CYP enzymes. Additionally, MLN0128 did not inhibit P-glycoprotein (P-gp) but did inhibit breast cancer resistance. At the plasma concentrations expected with the 40 mg dose of MLN0128, there exists a risk for a drug-drug interaction (DDI) with substrates of breast cancer-resistant protein (BCRP) (eg, methotrexate, irinotecan, rosuvastatin, topotecan, lapatinib, imatinib, etc.). Such agents should be avoided from co-administration with MLN0128. Since MLN0128 is metabolized by various CYP enzymes, the risk for clinically significant DDI (2-fold or greater) is considered low; however, given that the 40 mg dose of MLN0128 is the single agent MTD in the every week (QW) dosing schedule, potent inhibitors of CYP3A4 and CYP2C19 enzymes and strong inducers of CYP enzymes should not be administered concomitantly with MLN0128.
Amended or new wording:	**Recently completed in**-vitro-**metabolism experiments in human hepatocytes using ^{14}C-labeled** MLN0128 **suggest that, MLN0128** is metabolized ~~by various~~ **primarily via CYP1A2 (approximately 31% to 40%), with a minor contribution from CYP3A4 (approximately 11% to 22%). These data suggest that MLN0128 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyltransferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 metabolism**. ~~cytochrome P450 (CYP) enzymes, including 2C19 (35%), 3A4 (28%), and 2C9 (28%); MLN0128 neither~~

~~inhibited nor induced any of the major CYP enzymes. Additionally, MLN0128 did not inhibit P-glycoprotein (P-gp) but did inhibit breast cancer resistance. At the plasma concentrations expected with the 40 mg dose of MLN0128, there exists a risk for a drug-drug interaction (DDI) with substrates of breast cancer resistant protein (BCRP) (eg, methotrexate, irinotecan, rosuvastatin, topotecan, lapatinib, imatinib, etc.). Such agents should be avoided from co-administration with MLN0128.~~

~~Since MLN0128 is metabolized by various CYP enzymes, the risk for clinically significant DDI (2-fold or greater) is considered low; however, given that the 40 mg dose of MLN0128 is the single agent MTD in the every week (QW) dosing schedule, potent inhibitors of CYP3A4 and CYP2C19 enzymes and strong inducers of CYP enzymes should not be administered concomitantly with MLN0128.~~ **In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers (see Section 0) should only be administered with caution and at the discretion of the investigator during the study. Alternative treatments, if available, should be considered.**

Rationale for Change:

This paragraph was amended to describe updated data on MLN0128 metabolism by specific CYP isoforms.

Change 4: Update the list of relevant CYP inhibitors and inducers.

The primary change occurs in Section 14.4 List of Relevant Cytochrome P450 Inhibitors and Inducers:

Description of the change:	The list of relevant CYP inhibitors and induces was updated to remove sections listing strong CYP2C19 inhibitors and strong CYP3A4 inhibitors; to add section listing strong and moderate CYP1A2 inhibitors; and update the section listing clinically significant enzyme inducers.

Rationale for Change:

This change was made for consistency with updated data on MLN0128 metabolism by specific CYP isoforms.

Change 5: Remove the dietary restrictions related to CYP inhibitors and inducers.

The primary change occurs in Section 6.7 Precautions and Restrictions:

Deleted text:	Dietary restrictions include periods of fasting as described in Section 7.4.16, and in-home daily fasting glucose monitoring (refer to Section 7.4.18)**.** ~~not consuming food or beverages containing the fruit or juices listed in Section~~

~~14.4 within 1 week before first dose of study drug and throughout the study.~~

Rationale for Change:

This change was made for consistency with new data that removes the necessity for restrictions concerning CYP2C9 and 2C19.

Section 14.4 List of Relevant Cytochrome P450 Inhibitors and Inducers also contains this change.

Change 6: Insert language to reduce the required frequency of radiographic disease assessments for patients who have received at least 1 year of continuous MLN0128 treatment per protocol.

The primary change occurs in footnote "f" in the Schedule of Events:

Added text: **For long term patients, defined as study participation (greater than or equal to) 1 year, a CT (with contrast)/MRI of chest, abdomen, and pelvis will be obtained at intervals of up to every 4 cycles (plus or minus 7 days) as clinically indicated.**

Rationale for Change:

The change was made to reduce the burden and to minimize radiation exposure for long-term patients.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	04-Dec-2017 19:14 UTC