Title: An Open-Label, Phase 1b/2 Study Investigating Recommended Phase 2 Dose, Safety, Tolerability, and Preliminary Efficacy of TAK-659 in Adult Patients With Relapsed or Refractory Acute Myelogenous Leukemia (AML)

NCT Number: NCT02323113

Protocol Approve Date: 05 January 2018

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

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL C34002 AMENDMENT 02

TAK-659

An Open-Label, Phase 1b/2 Study Investigating Recommended Phase 2 Dose, Safety, Tolerability, and Preliminary Efficacy of TAK-659 in Adult Patients With Relapsed or Refractory Acute Myelogenous Leukemia (AML)

Protocol Number:	C34002
Indication:	Relapsed and/or refractory AML
Phase:	1b/2
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original	24 September 2014
Amendment 01	15 June 2015
Amendment 02	05 January 2018

Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA USA 02139
Telephone: +1 (617) 679-7000

Approved by:

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

PPD

Rationale for Amendment 02

The main reasons for Amendment 02 are to update the risks (and associated changes throughout), clarify twice daily (BID) dosing, and to remove the pS6 secondary endpoint.

Purposes for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment 02. The primary reason for this amendment is to update the original protocol to comply with Takeda standards and standard operating procedures.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. The purposes of this amendment are:

- To replace signatories who were previously assigned to the protocol.
- To update the proposed number of patients in the study.
- To update language specifying inclusivity of the tyrosine kinase domain mutant populations.
- To clarify TAK-659 dosage can include BID dosing.
- To remove the PD effects of TAK-659 (due to the removal of the pS6 sample) and the PD assessment from secondary endpoints, Schedule of Events, Overview of Study, and Study Design.
- To update the dose escalation status of Study C34001 and specify the maximum tolerated dose (MTD) as 100 mg.
- To allow for prior exposure to investigational FLT-3 inhibitors in the phase 2 portion of the study.
- To add creatine phosphokinase (CPK) testing to the Schedule of Events.
- To add cytomegalovirus (CMV) testing to the Schedule of Events.
- To update title of Assessment Schedule.
- To specify time of day for BID dosing.
- To remove specification that subsequent anticancer therapy should not be initiated before recovery from all treatment-emergent toxicities associated with TAK-659.
- To update TAK-659 50% inhibition concentration.
- To update information on the nonclinical experience of TAK-659.
- To update information on the clinical experience of TAK-659.
- To update details for the PK CCI [redacted].
- To update the risks of TAK-659 in nonclinical and clinical studies.
- To update the number of patients and study centers.
- To update the study duration.
- To update contraception methods.
- To update laboratory values regarding lipase and amylase, and to exclude patients with moderate renal impairment.

- To clarify exclusion criteria of systemic anticancer treatment.
- To clarify exclusion criteria regarding use or consumption of substances (medication and supplements).
- To update TAK-659 dose adjustments for nonhematologic toxicities.
- To provide updates to concomitant medications and procedures.
- To provide details on managing pneumonitis, edema, hypophosphatemia, enzyme elevations (including transaminase, amylase and lipase, and CPK elevations, in addition to lactate dehydrogenase elevations).
- To provide updated details on managing infections.
- To provide updated details on managing rash with or without pruritus.
- To update temperature of storage conditions to make consistent with other protocols.
- To update language for concomitant medications and procedures.
- To update clinical laboratory evaluations to reflect addition of CMV testing.
- To clarify PD population will be derived from the plasma inhibitory assay.
- To remove the PD assessment from the PK analysis.
- To update product complaint telephone number.
- To add CRp, CRh, and CRc to the definition of a response for purposes of disease assessment.

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

PROTOCOL SUMMARY

Study Title: An Open-Label, Phase 1b/2 Study Investigating Recommended Phase 2 Dose, Safety, Tolerability, and Preliminary Efficacy of TAK-659 in Adult Patients With Relapsed or Refractory Acute Myelogenous Leukemia (AML)

Number of Patients:

Phase 1b dose finding phase: approximately 40 patients

Phase 2 expansion phase: up to 66 based on a Simon's 2-Stage design in both FLT-3 wild type (WT) and FLT-3-internal tandem duplication (ITD) mutant populations (inclusive of the tyrosine kinase domain [TKD] mutant populations)

Study Objectives

Primary

- Phase 1b dose finding phase: to determine the safety, tolerability, and maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of TAK-659 administered orally on a once daily (QD) or twice daily (BID) dosing schedule in patients with relapsed or refractory AML
- Phase 2 expansion phase: to evaluate preliminary efficacy of TAK-659 in relapsed or refractory AML as measured by overall response rate (ORR)

Secondary

- To evaluate additional efficacy measures of TAK-659, such as duration of response (DOR), time to progression (TTP), mortality rate at 3 and 6 months, and overall survival (OS)
- To evaluate differential efficacy of TAK-659 in patients with or without FLT-3-ITD/TKD mutation
- To characterize the plasma pharmacokinetics (PK) of TAK-659 in patients with relapsed or refractory AML

Exploratory

CCI

[redacted]

Overview of Study Design: This study will include a phase 1b dose finding portion and a single-arm phase 2 expansion portion in relapsed or refractory AML.

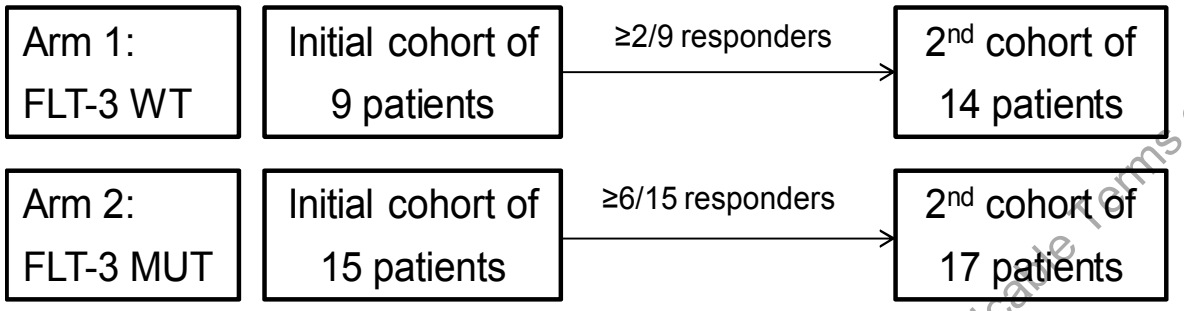
The starting dose for the phase 1b portion of this study (Study C34002) will be directed by the current Study C34001, the first-in-human (FIH) dose escalation study of TAK-659 in patients with advanced solid tumors and lymphoma. The starting dose in Study C34002 will not exceed the highest dose determined to be safe in Study C34001 at the time Study C34002 starts. A dose of 60 mg QD was determined to be tolerable based on a 3+3 dose escalation schema after evaluation of 6 patients. Based on these data, the starting dose will be 60 mg QD for Study C34002. Since the initiation of Study C34002, dose escalation has been completed in Study C34001 with 100 mg QD determined as the MTD. In the expansion phase of the ongoing FIH study, lymphoma patients are being evaluated at 100 mg and early clinical activity has been observed in this population. In the Non Hodgkin Lymphoma population, the more relevant target for TAK-659 is SYK.

A 3+3 dose escalation design will be used to determine the MTD of TAK−659 in AML. Each 28-day treatment cycle will be composed of 28 consecutive days of QD or BID TAK-659 treatment. Planned dose escalation will follow 20-mg increments of escalation (eg, from 60 mg to 80 mg QD or BID). A more aggressive dose escalation (more than 20-mg increments but not exceeding 100% escalation), evaluation of alternative regimens, and expansion of an existing dose level up to 12 evaluable patients are all permissible following discussions between the sponsor and the investigators based on evolving safety, tolerability, and PK data of TAK-659. Dose escalation will continue until either MTD is reached or the RP2D (if different from MTD) has been determined based on safety, tolerability, PK, and preliminary efficacy data, if available. At least 6 patients will be evaluated at RP2D (either the MTD or at a lower dose as determined) before making a decision to advance to the phase 2 expansion phase. In the process of determining or refining RP2D, expansion of more than 1 dose level to at least 6 patients (up to a maximum of 12 evaluable patients per dose level) is permissible so that early signs of clinical activity can be assessed to a greater extent to assist dose selection.

The phase 2 expansion study in relapsed or refractory AML will be conducted using a Simon's 2-stage design. The objectives of this phase 2 stage of the study are to evaluate longer-term safety and tolerability of TAK-659 administered at the RP2D and to detect any efficacy signal that warrants further development of TAK-659 in AML. The primary measure of efficacy for the phase 2 portion will be the ORR, which will include complete response (CR), CR with incomplete platelet recovery (CRp), CR with incomplete hematologic recovery (CRi), CR with partial hematologic recovery (CRh), a composite complete remission (CRc defined as the sum of a patient achieving a CR, CRh, CRi, or CRp), and partial response (PR). Nine and 15 response-evaluable patients will be enrolled initially in the FLT-3 WT and FLT-3 ITD/TKD mutant cohorts, respectively, during the first stage. Best response will be assessed by the end of Cycle 4 of TAK-659 treatment for the purpose of an interim analysis between Stage 1 and Stage 2. The FLT-3 WT and FLT-3 ITD/TKD mutant cohorts will proceed to the second stage if ≥2 and ≥6 patients, respectively, respond to treatment (ORR). Other efficacy measures, such as DOR, TTP, and mortality rate will also be considered in the decision to expand the study to the second stage. If the FLT-3 WT and/or FLT-3 ITD/TKD mutant cohort(s) proceed(s) to the second stage, a further 14 and 17 evaluable patients will be assessed in the 2 cohorts, respectively. Best responses from both cohorts will be assessed individually and combined in an effort to understand the all-comer response rate. Retrospective analysis will be performed to identify potential patient selection markers either based on levels of baseline activation or posttreatment modulation of FLT-3 and SYK, the 2 targets of TAK-659. Analysis for mutations reported for AML will also be performed.

Study Population: Patients will be males and females age 18 years or older with histopathologically documented primary or secondary AML (excluding acute promyelocytic leukemia) as defined by World Health Organization (WHO) criteria, for whom no standard therapies are anticipated to result in a durable remission based on the opinion of the investigator, or who refuse standard therapies. For the phase 2 portion of the study, patients must be refractory to or relapsed after no more than 2 prior chemotherapy regimens. Patients must have adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients must not have clinically significant toxicity from prior chemotherapy, hematopoietic stem cell transplant (HSCT) within 60 days of the first dose of TAK-659, or clinically significant graft-versus-host disease requiring ongoing immunosuppressive therapy.
Duration of Study: It is anticipated that this study will last for approximately 66 to 72 months, including 34 to 36 months in the phase 1b portion and 32 to 36 months in the phase 2 portion.

STUDY OVERVIEW DIAGRAM (PHASE 2 DOSE EXPANSION)



Abbreviations: MUT = mutation; WT = wild type

SCHEDULE OF EVENTS

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

	Screening[a]	Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1		
Dosing												
TAK-659 administration[d]		TAK-659 is dosed orally once or twice daily every day										
Study Procedures												
Informed consent[e]	X											
Inclusion/exclusion criteria	X											
Demographics and disease characteristics	X											
Complete medical history[f]	X	X										
Modified Charlson Comorbidity Index Assessments	X[g]											
Physical examination[f]	X	X		X	X		X	X	X	X	X	
Height	X											
Weight[h]	X	X						X		X	X	
Vital signs[i]	X	X		X	X		X	X	X	X	X	
ECOG performance status	X	X						X		X	X	
12-lead ECG[j]	X	X			X			X		X	X	

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

	Screening[a]	Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1		
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first										
Adverse event reporting		Recorded from first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first										
	Serious adverse events[k] will be reported from signing of the informed consent form through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy											
Patient diary review[l]		X		X	X		X	X	X	X	X	
Response Assessments												
Bone marrow biopsy and aspirate for disease response monitoring	X[m]						X[m]		X[m]			
Samples/Laboratory Assessments												
Pregnancy test[n]	X	X						X		X		
Hematology/ Chemistry[o,p]	X	X		X	X		X	X	X	X	X	
CPK testing[o,p]	X	X		X	X		X	X	X	X	X	
Urinalysis (for hematuria and proteinuria evaluation)[p,q]	X				X			X		X		
Ophthalmic Exam[r]	X							X[r]		X[r]	X	

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

	Screening[a]	Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1		
CCI [redacted]												
Blood sample for FLT-3 mutation analysis[t]	X											
CCI [redacted]												
Blood sample for plasma inhibitory assay[v]		X			X			X[v]	X[v]			
CCI [redacted]												
Blood samples for PK[z]		X	X		X	X						
Survival Follow Up Contact [c]												X
CMV testing[aa]	X											

Abbreviations: AML = acute myelogenous leukemia; CPK= creatine phosphokinase; CxDx = Cycle x, Day x; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; P-gp = P-glycoprotein; PK =pharmacokinetic(s).

Evaluations/laboratory assessments performed on visit days need to take place before dosing unless otherwise indicated. On these days, patients should be instructed to hold dosing until relevant assessments have been completed.

a Screening assessments are performed within 28 days before the Cycle 1, Day 1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

b End of Study visit will occur 28 days (+ 10 days) after the last dose of study drug or before the start of subsequent anticancer therapy (other than

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

	Screening[a]	Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1		

hydroxyurea) if that occurs sooner.

c All patients, including those patients no longer on treatment, will be assessed for survival. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every month until death, loss to follow-up, or withdrawal of consent for further follow-up for up to 12 months after discontinuation of the study drug. In addition, information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who achieve CR but discontinue study treatment while still in remission, disease progression based upon available local data will also be collected during the survival follow-up period.

d TAK-659 will be administered orally once or twice daily for 28-day cycles. The option to modify the schedule of drug administration to include alternative schedules will be based on the review of the available PK, safety, and other clinical data by the investigators and the sponsor.

e Informed consent may be obtained before the Screening period (28 days before Cycle 1, Day 1 dosing).

f The Cycle 1, Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1, Day 1). Complete physical examinations will be performed during screening and will include a neurological exam. Complete physical exams will also be performed on Day 1 of each cycle, and at the End of Study (EOS) visit. Symptom- or finding-directed physical examination will be performed on Days 8, 15, and 22 of Cycle 1 and Day 15 of Cycles 2, 3, and 4.

g See Section 14.1 for Modified Charlson Comorbidity Index.

h Weight should be obtained at screening, on Day 1 predose of each cycle, and at EOS.

i Vital signs measurement (blood pressure, heart rate, and temperature) should be performed before dosing on visit days and as clinically indicated.

j In Cycle 1, single 12-lead ECGs will be performed as detailed in the AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule. For Cycle 2 and beyond, the ECGs will be performed only on Day 1 predose.

k Serious adverse event (SAE) reporting will include serious pretreatment events. Only those SAEs that occur after the first dose of study drug will be collected in the eCRF. However, all SAEs occurring after consent will be reported to the Millennium Department of Pharmacovigilance or designee (see Section 9.2).

l The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

m Bone marrow biopsy and aspirate assessments of disease burden (blast counts), cytogenetics, and cellular composition by flow cytometry will be performed at screening. In addition, bone marrow biopsies and/or aspirates will be collected to assess disease response between Days 22 and 28 of Cycles 1, 2, and 4, provided that the disease assessment is available before Day 1 of the following cycle. Beyond Cycle 4, bone marrow biopsy and/or aspirate assessment will be performed as clinically indicated based on changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. Note that a bone marrow biopsy is required only at screening. Residual and/or additional bone marrow samples will be requested for biomarker analysis as well as confirmation of the FLT-3 mutation status. See footnotes w, x, y and Section 7.4.15.1 for further details.

n A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 may be administered for that cycle. If a serum pregnancy test is performed

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

	Screening[a]	Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1		

within 3 days of dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1, Day 1.

o The hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. The percentage of leukemic blast cells should also be noted in the hematology panel. If screening clinical laboratory testing was performed within 3 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1. The percentage of leukemic blast cells should also be noted in the hematology panel.

p Laboratory assessments can be conducted within - 3 days of the scheduled visit, with the exception of PK/plasma inhibitory assay assessments or unless otherwise noted. Day 1 visits of Cycle 2 and beyond may be modified by up to 3 days due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).

q Urinalysis samples will be collected predose and analyzed at the site's local laboratory.

r An ophthalmic exam should be performed at screening, on Cycle 2, Day 1, on Cycle 7, Day 1, every 6 cycles thereafter (± 2 weeks), and at EOS. See Section 7.4.14 for details.

s CCI [redacted]

t A peripheral blood sample will be obtained at screening for confirmation of the FLT-3 mutation status by a central laboratory test designated by the sponsor.

u CCI [redacted]

v Blood specimens will be collected for assessment of the FLT-3 and potentially SYK inhibitory effects of TAK-659 in vitro by plasma inhibitory assay. Time points for this blood collection are predose on Cycle 1, Day 1, Cycle 2, Day 1, Cycle 1, Day 15, and Cycle 2, Day 15.

w Additional bone marrow aspirates (remaining aspirate material from the first pull or a second or third pull of bone marrow aspirate) and biopsy specimens (segments of the first core biopsy or additional core biopsies) after taking specimens for disease assessment (see footnote m) will be collected during screening for confirmation of the FLT-3 mutation status and exploratory biomarker studies. Note that if a standard of care bone marrow biopsy and aspirate have already been performed on a patient within 28 days of Day 1 of Cycle 1, additional bone marrow biopsy and aspirate need not be repeated if results are available for disease assessment purposes. However, if the site has access to these samples and adequate residual material remains, these samples should be sent to the Sponsor-designated laboratory(ies). See the Laboratory Manual for details about the sample collection and shipment procedures. If only one specimen (biopsy or aspirate) has already been performed within 28 days of Day 1 of Cycle 1, please discuss with study sponsor.

x If adequate residual material is available from bone marrow aspirates and/or biopsies collected for disease assessment (or as clinically indicated) during the

Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]

		Cycle 1						Cycles 2, 3, and 4		Cycles 5, 6, and beyond		
	Screening[a]	Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 1	EOS[b] (+10 days)	Survival Follow-up[c]

study period (from first dose to 28 days after discontinuation of study treatment), these samples are requested to be sent to the Sponsor-designated laboratory(ies) for biomarker studies. See Section 7.4.15.1 for further details.

y At the time of relapse of any patient who had initially responded to TAK-659, bone marrow aspirate and/or biopsy materials will be collected for biomarker study. See Section 7.4.15.1 for further details.

z Blood specimens for PK plasma samples will be collected at time points specified in the AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule. Refer to the Laboratory Manual for detailed instructions on collection, processing, storing, and shipping of PK samples.

aa Blood specimen will be collected during screening for a local polymerase chain reaction testing of CMV replication. The CMV viral load data will be entered in the eCRF. Further monitoring of CMV, if indicated, will follow the local standard practice.

AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule: Cycle 1

	Cycle 1							
	Day 1			Day 2 (24 hours post Day 1 dose ± 1 hour)[a,b]	Day 15[a,b]			Day 16 (24 hours post Day 1 dose ± 1 hour)[a,b]
	Single ECG	PK	PIA[c]	PK	Single ECG	PK	PIA	PK
Predose (within 1 hour before dosing)	X	X	X	X	X	X	X	X
0.5 hour postdose (± 10 min)		X				X		
1 hours postdose (± 10 min)		X				X		
2 hours postdose (± 10 min)		X				X		
3 hours postdose (± 30 min)	X	X			X	X		
4 hours postdose (± 30 min)		X				X		
8 hours postdose (± 30 min)		X				X		

Abbreviations: AML = acute myelogenous leukemia; CXDY = Cycle X, Day 1; ECG = electrocardiogram; h = hour(s); min = minutes; PIA = plasma inhibitory assay; PK = pharmacokinetic.

When the timing of a PK, PIA, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples. For BID dosing, PK, PIA, and ECG assessment schedule refers to the AM dose.

a Instruct the patient to arrive at the clinic without taking his/her study drug dose for that day.

b The timing of the visit should be planned so that the predose assessments occur at approximately the same time as the dosing time on the previous day(s).

c PIA samples are also obtained on Days 1 and 15 in Cycle 2 (see Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles] footnote v).

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]

	Screening[a]	Cycle 1					Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+ 10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Dosing											
TAK-659 administration[d]		TAK-659 is dosed orally once or twice daily every day									
Study Procedures											
Informed consent[e]	X										
Inclusion/exclusion criteria	X										
Demographics and disease characteristics	X										
Medical history[f]	X	X									
Modified Charlson Comorbidity Index Assessments	X[g]										
Physical examination[f]	X	X		X	X	X	X	X	X	X	
Height	X										
Weight[h]	X	X					X		X	X	
Vital signs[i]	X	X		X	X	X	X	X	X	X	
ECOG performance status	X	X					X		X	X	
12-lead ECG[j]	X	X					X		X	X	

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]

	Screening[a]	Cycle 1					Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+ 10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first									
Adverse event reporting		Recorded from first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first									
	Serious adverse events[k] will be reported from signing of the informed consent form through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy										
Patient diary review[l]		X		X	X	X	X	X	X	X	
Response Assessments											
Bone marrow biopsy and aspirate for disease response monitoring	X[m]					X[m]		X[m]			
Samples/Laboratory Assessments											
Pregnancy test[n]	X	X					X		X		
Hematology/ Chemistry[o,p]	X	X		X	X	X	X	X	X	X	
CPK Testing[o,p]	X	X		X	X	X	X	X	X	X	
Urinalysis (for hematuria and proteinuria evaluation)[p,q]	X						X		X	X	
Ophthalmic Exam[r]	X						X[r]		X[r]	X	

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]

	Screening[a]	Cycle 1					Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+ 10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		
CCI [redacted]											
Blood sample for FLT-3 mutation analysis[t]	X										
CCI [redacted]											
Blood sample for PK[y]		X			X						
Survival Follow Up Contact [c]											X
CMV testing[z]	X										

Abbreviations: AML = acute myelogenous leukemia; CPK= creatine phosphokinase; CxDx = Cycle x, Day x; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; PK =pharmacokinetic(s)

Evaluations/laboratory assessments performed on visit days need to take place before dosing unless otherwise indicated. On these days, patients should be instructed to hold dosing until relevant assessments have been completed.

a Screening assessments are performed within 28 days before the Cycle 1, Day 1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

b End of Study visit will occur 28 days (+ 10 days) after the last dose of study drug or before the start of subsequent anticancer therapy (other than hydroxyurea) if that occurs sooner.

c All patients, including those patients no longer on treatment, will be assessed for survival. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every month until death, loss to follow-up, or withdrawal of consent for further follow-up for up to 12 months after discontinuation of the study drug. In addition, information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who achieve CR but discontinue study treatment while still in remission, disease progression based upon available local data, will also

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]

		Cycle 1					Cycles 2, 3, and 4		Cycles 5, 6, and beyond		
	Screening[a]	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	EOS[b] (+ 10 days)	Survival Follow-up[c]

be collected during the survival follow-up period.

d TAK-659 will be administered orally once or twice daily for 28-day cycles. The option to modify the schedule of drug administration to include alternative schedules will be based on the review of the available PK, safety, and other clinical data by the investigators and the sponsor.

e Informed consent may be obtained before the Screening period (28 days before Cycle 1, Day 1 dosing).

f The Cycle 1, Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1, Day 1). Complete physical examinations will be performed during screening and will include a neurological exam. Post screening physical exams will be symptom- or finding-directed.

g See Section 14.1 for Modified Charlson Comorbidity Index.

h Weight should be obtained at screening, on Day 1 predose of each cycle, and at EOS.

i Vital signs measurement (blood pressure, heart rate, temperature) should be performed before dosing on visit days and as clinically indicated.

j Single 12-lead ECGs will be performed at screening, predose on Day 1 of each cycle, and EOS. When the timing of a blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.

k Serious adverse event (SAE) reporting will include serious pretreatment events. Only those SAEs that occur after the first dose of study drug will be collected in the eCRF. However, all SAEs occurring after consent will be reported to the Millennium Department of Pharmacovigilance or designee (see Section 9).

l The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

m Bone marrow biopsy and aspirate assessments of disease burden (blast counts), cytogenetics, and cellular composition by flow cytometry will be performed at screening. In addition, bone marrow biopsies and/or aspirates will be collected to assess disease response between Days 22 and 28 of Cycles1, 2, and 4, provided that the disease assessment is available before Day 1 of the following cycle. Beyond Cycle 4, bone marrow biopsy and/or aspirate assessment will be performed as clinically indicated based on changes in peripheral blood counts or when it is needed to establish either CR or disease progression. Note that a bone marrow biopsy is required only at screening. Residual and/or additional bone marrow samples will be requested for biomarker analysis as well as confirmation of the FLT-3 mutation status. See footnotes v, w, x and Section 7.4.15.1 for further details.

n A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test must be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 may be administered for that cycle. If a serum pregnancy test is performed within 3 days of dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1, Day 1.

o The hematology and chemistry blood samples for Cycle 1, Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. The percentage of leukemic blast cells should also be noted in the hematology panel. If screening clinical laboratory testing was performed within 3 days before the Cycle 1, Day 1 dose, it need not be repeated on Cycle 1, Day 1. The percentage of leukemic blast cells should also be noted in the hematology panel.

p Laboratory assessments can be conducted within - 3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise noted. Day 1 visits of Cycle 2 and beyond may be modified by up to 3 days due to extenuating circumstances (ie, inclement weather, holidays,

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]

	Screening[a]	Cycle 1					Cycles 2, 3, and 4		Cycles 5, 6, and beyond	EOS[b] (+ 10 days)	Survival Follow-up[c]
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1		

vacations, or other administrative reasons).

q Urinalysis samples will be collected predose and analyzed at the site's local laboratory.

r An ophthalmic exam should be performed at screening, on Cycle 2, Day 1, on Cycle 7, Day 1, every 6 cycles thereafter (± 2 weeks), and at EOS. See Section 7.4.14 for details.

s CCI [redacted]

t A peripheral blood sample will be obtained at screening for confirmation of the FLT-3 mutation status by a central laboratory test designated by the sponsor.

u CCI [redacted]

v Additional bone marrow aspirates (remaining aspirate material from the first pull or a second or third pull of bone marrow aspirate) and biopsy specimens (segments of the first core biopsy or additional core biopsies) after taking specimens for disease assessment (see footnote m) are required during screening for confirmation of the FLT-3 mutation status and exploratory biomarker studies. See Section 7.4.15.1 for further details and the Laboratory Manual for details about the sample collection and shipment procedures.

w If adequate residual material is available from bone marrow aspirates and/or biopsies collected for disease assessment (or as clinically indicated) during the study period (from first dose to 28 days after discontinuation of study treatment), these samples are requested to be sent to the Sponsor-designated laboratory(ies) for biomarker studies. See Section 7.4.15.1 for further details.

x At the time of relapse of any patient who had initially responded to TAK-659, bone marrow aspirate and/or biopsy materials will be collected for biomarker study. See Section 7.4.15.1 for further details.

y Blood specimens for PK plasma samples will be collected at time points specified in the AML Dose Expansion (Phase 2) PK Schedule. Refer to the Laboratory Manual for detailed instructions on collection, processing, storing, and shipping of PK samples.

z Blood specimen will be collected during screening for a local polymerase chain reaction testing of CMV replication. The CMV viral load data will be entered in the eCRF. Further monitoring of CMV, if indicated, will follow the local standard practice.

AML Dose Expansion (Phase 2) PK Schedule: Cycle 1

	Cycle 1	
	Day 1	**Day 15[a,b]**
	PK[c]	**PK[c]**
Predose (within 1 hour before dosing)	X	X
2-4 hours postdose	X	X

Abbreviations: AML = acute myelogenous leukemia; CXDY = Cycle X, Day 1; h = hour(s); min = minutes; PK = pharmacokinetic. For BID dosing, PK schedule refers to the AM dose.

a Instruct the patients to arrive at the clinic without taking his/her study drug dose for that day.

b The timing of the visit should be planned so that the predose assessments occur at approximately the same time as the dosing time on the previous days.

c Residual plasma from PK samples collected at scheduled sampling time points in the expansion cohorts may be used for PIA assessments, if determined to be appropriate by the sponsor.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC_∞	area under the plasma concentration versus time curve from zero to infinity
AUC_τ	Area under the plasma concentration versus time curve over the dosing interval
BID	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CD	compact disc
CI	confidence interval
CL/F	apparent clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum (peak) plasma concentration
CMV	cytomegalovirus
CO_2	carbon dioxide
CPK	creatine phosphokinase
CR	complete response
CRc	composite complete remission
CRh	complete response with partial hematologic recovery
CRi	complete response with incomplete recovery of blood counts
CRO	contract research organization
CRp	complete response without platelet recovery
CYP	cytochrome P_{450}
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation	Term
DOR	duration of response
EC_{50}	Concentration producing half-maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
FDA	United States Food and Drug Administration
FIH	first-in-human
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	γ-glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
GVHD	graft-versus-host disease
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activating motifs
ITD	internal tandem duplication
IV	intravenous; intravenously
IWG	International Working Group
LC/MS/MS	liquid chromatography tandem mass spectrometry
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non Hodgkin lymphoma
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
CCI [redacted]	
P-gp	P-glycoprotein
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic(s)
PR	partial response
CCI [redacted]	
PTR	peak-trough ratio
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
Rac	accumulation ratio
RP2D	recommended phase 2 dose
RBC	red blood cell
SAE	serious adverse event
$t_{1/2z}$	terminal disposition phase half-life
TKD	tyrosine kinase domain
t_{max}	first time to reach maximum (peak) plasma concentration
TTP	time to progression
ULN	upper limit of the normal range
WHO	World Health Organization
WT	wild type

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Acute myelogenous leukemia (AML) is a heterogeneous disorder of the hematopoietic progenitor cells of myeloid lineage, characterized by a block in differentiation and uncontrolled proliferation. The majority of patients with AML are older than 60 years of age. The median age at diagnosis is between 65 and 70 years [2], and approximately 35% of patients with newly diagnosed AML are 75 years of age or older [3]. AML as a family of heterogeneous malignancies can be categorized using the World Health Organization (WHO) classification system based on a combination of morphology, immunophenotype, genetics, and clinical features. In addition to clinical risk factors such as age, performance status, and whether AML is associated with prior therapy or antecedent hematologic disorders, cytogenetic and molecular features have been found to have major prognostic importance. For example, data suggest that the presence of *FLT-3* gene mutations negatively impacts response to standard therapy and disease outcome.

Treatment of AML requires initial induction chemotherapy with the goal of achieving complete remission (CR) with resolution of morphologically detectable disease and restoration of normal blood counts. Intensive combination chemotherapy is the primary modality for induction therapy for AML. Options usually include standard or high-dose cytarabine (also referred to as Ara-C) in combination with an anthracycline. Most remissions require only a single course; however, approximately one-quarter to one-third of patients will require a second induction cycle to obtain a complete remission.

Post-remission therapy, with the aim of prolonging the initial CR and eradicating minimal residual disease, has traditionally entailed further chemotherapy, typically 2 to 4 courses of consolidation therapy, with or without subsequent prolonged lower dose maintenance therapy. Disease reoccurs in the majority of patients, with only a small likelihood of potential cure after administration of "salvage" therapy. Allogeneic stem cell transplantation has been used to overcome this problem, and showed a higher cure and disease control rate. However, it is associated with a higher risk of treatment-related morbidity and mortality and is not appropriate for many patients. In addition, patients who relapse within 6 months of initial chemotherapy do not do as well after allogeneic stem cell transplant as those with longer initial responses [4].

The CR rate achieved after standard induction therapy is reported to be between 45% and 60%. However, the probability of remaining in remission 3 years after diagnosis is below 10%, the median overall survival (OS) is between 5 and 10 months, and the 5-year survival rate is between 6% and 12% [2]. These already disappointing results are still likely to overestimate the efficacy of chemotherapy in elderly patients because most studies included only patients considered to be medically fit [2].

AML represents a significant unmet medical need. Despite great progress made in the understanding of the molecular basis for the heterogeneity of the disease, the standard of care has not changed in decades. There is a dire need for alternative or additional therapeutic options for patients with this deadly disease.

1.1.2 Study Drug

TAK-659 is a reversible, potent, dual inhibitor of SYK and FLT-3 being developed for oncology indications, the pathogenesis of a subset of tumors being driven by SYK- and/or FLT-3-mediated signaling. TAK-659 inhibits purified SYK and FLT-3 enzymes with concentrations producing 50% inhibition (IC_{50}) of 3.2 and 4.6 nM, respectively. In cultured human tumor cells, TAK-659 potently inhibited the growth of hematopoietic-derived cell lines, with a concentration producing half-maximal response (EC_{50}) ranging from 11 to 775 nM in sensitive cell systems (eg, T-cell lymphoblastoma, megakaryoblastoma, and AML). In a broad kinase panel, TAK-659 demonstrated a more than 50-fold selectivity for SYK and FLT-3 over 290 other protein kinases screened.

1.2 Nonclinical Experience

CCI

[redacted]

Detailed information regarding the nonclinical pharmacology and toxicology of TAK-659 may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

As of 05 September 2017, 181 patients have been dosed with TAK 659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001 (advanced solid tumors and lymphoma), 32 patients in Study C34002 (R/R AML), 19 patients in Study C34003 (advanced solid tumor), and 9 patients in Study C34005 (advanced NHL). Both the C34001 and C34002 studies are evaluating TAK-659 as a single agent, while the C34003 and C34005 studies are evaluating TAK-659 in combination with nivolumab (C34003) and 5 additional combination agents (C34005). Different data cutoff dates were used to provide the most current clinical information, given that the ongoing studies are in various stages of conduct. The most current safety and efficacy data for Study C34001 are from the 02 June 2017 data cutoff date. The most current safety and efficacy data for Study C34002 are from the 24 May 2017 data cutoff date. In Study C34003, the TAK-659 dose has been evaluated across 3 dose levels of 60 mg, 80 mg, and 100 mg and the maximum tolerated dose (MTD) determination is pending. In Study C34005, TAK-659 is currently being evaluated at 60 mg with plans to escalate to 100 mg.

1.3.1 Ongoing Studies With TAK-659

As of 05 September 2017, 181 patients have been dosed with TAK 659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001, 32 patients in Study C34002, 19 patients in Study C34003, and 9 patients in Study C34005.

Study C34001: As of 02 June 2017, the TAK-659 dose was escalated from 60 mg to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [90 patients], and 120 mg [7 patients]). The MTD for patients with lymphoma and solid tumors has been determined to be 100 mg once daily (QD). Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 111 patients treated in this study (92 patients with lymphoma, including 5 patients with chronic lymphocytic leukemia [CLL] and 19 patients with solid tumors), 96 patients had discontinued from study by the June 2017 data cutoff date. The reasons for discontinuation included PD (45 patients), adverse events (AEs) (29 patients), symptomatic deterioration (13 patients), initiation of hematopoietic stem cell transplant (2 patients), protocol violation (1 patient), withdrawal by subject (1 patient), and other (5 patients).

Study C34002: As of 24 May 2017, 31 patients had enrolled. TAK-659 has been escalated from 60 mg QD to 160 mg QD, and an additional dose level of 80 mg BID is also being

evaluated. The MTD/RP2D has not yet been determined. Of the 31 patients treated in this study, 28 patients had discontinued from the study as of the May 2017 data cutoff date. The reasons for discontinuation included PD (5 patients), AEs (18 patients), symptomatic deterioration (2 patients), withdrawal by subject (1 patient), and other (2 patients).

The reported AEs were generally as expected on the basis of nonclinical toxicology findings of TAK 659 and the patient population being studied. As of 02 June 2017, the most common treatment-related AEs reported in Study C34001 (≥20% of patients) have been aspartate aminotransferase (AST) increased (49 patients [44%]), amylase increased (39 patients [35%]), lipase increased (31 patients [28%]), alanine aminotransferase (ALT) increased and diarrhea (28 patients each [25%]), blood creatinine phosphokinase (CPK) increased and hypophosphatemia (26 patients each [23%]), and fatigue (22 patients [20%]).

The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (23 patients [21%]), hypophosphatemia (18 patients [16%]), lipase increased (15 patients [14%]), neutropenia (14 patients [13%]), CPK increased (13 patients [12%]), anemia and AST increased (7 patients each [6%]), and pneumonia (5 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase increased, AST and ALT increased, and blood CPK increased. In Study C34001, as of 02 June 2017, there were 35 on-study deaths. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated varicella, and respiratory failure in the presence of Pneumocystis jiroveci pneumonia [PJP]; cytomegalovirus [CMV] and aspergillus infection; and right pneumothorax and renal failure).

In Study C34001, as of 02 June 2017, 9 of 48 response-evaluable patients with DLBCL achieved a complete response (CR) and 4 achieved a partial response (PR). Seven of 10 response-evaluable patients with indolent lymphomas responded (1 CR and 6 PRs). Two of 4 response-evaluable patients with CLL achieved a response (both PR).

In Study C34002, as of 24 May 2017, there were 15 on-study deaths (one drug-related, multiple organ dysfunction syndrome). To date, the safety profile in Study C34002 appears to be similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both peripheral blast and bone marrow blast counts. Three patients have achieved objective response per IWG 2003 criteria (1 CR, 2 CRi) [15] as of the cutoff date.

1.4 Study Rationale

TAK-659 is a selective, potent, dual inhibitor of FLT-3 and SYK.

FLT-3 is a Class III receptor tyrosine kinase that is normally expressed only in hematopoietic stem and progenitor cells. However, its expression has been found in the blasts of a majority of patients with AML. Activating mutations of FLT-3, including internal tandem duplication (ITDs) within the juxtamembrane region of FLT-3 and point mutations in the FLT-3 activation loop, are observed in approximately 30% of AML patients. These FLT-3 mutations, associated with early relapse after standard chemotherapy and poor survival, represent a critical prognostic factor for AML. The ligand-independent and constitutive activation of FLT-3 resulting from these gain-of-function mutations, promotes proliferation and survival of AML blasts through the STAT5, RAS/MAPK, and PI3K/AKT pathways. Therefore, FLT-3 is a rational drug target for AML. Several FLT-3 inhibitors have been explored clinically and potential therapeutic benefit in AML has been demonstrated.

SYK is a non-receptor protein tyrosine kinase that is broadly expressed in hematopoietic cells. SYK binds to phosphorylated immunoreceptor tyrosine-based activating motifs (ITAM) in key surface receptors in immune cells, including Fc, B cell, T cell, and certain natural killer cell receptors. SYK functions normally to mediate ITAM signaling by coupling activated immunoreceptors to downstream signaling events that mediate diverse cellular responses, including proliferation, differentiation, phagocytosis, and survival. The importance of SYK in hematological malignancies has been recognized in lymphoma, leukemia, and myelodysplastic syndrome (MDS). For example, recurrent ITK-SYK translocations have been reported in peripheral T-cell lymphoma, and SYK-dependent tonic B-cell receptor signaling has been recognized as an important survival pathway in DLBCL. Clinical trials demonstrating that SYK inhibition could lead to tumor responses in patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia, further established the relevance of SYK in B-cell malignancy.

A role for SYK in myeloid malignancies was first suggested with the report of a fusion of TEL to SYK in a patient with MDS with t(9;12) (q22;p12). Importantly, this TEL-SYK fusion transformed the interleukin-3 (IL-3)-dependent murine hematopoietic cell line Ba/F3 to growth factor independence. Additionally, AML was identified as another hematologic malignancy in which SYK plays an important role. Genetic and pharmacological

inactivations of SYK have been shown to promote differentiation of AML cells and attenuate leukemia growth in vivo.

A recently published study suggested that SYK is a critical regulator of FLT-3 in AML. FLT-3 was found to be transactivated by SYK via direct binding [6]. Highly activated SYK was predominantly found in FLT-3-ITD-positive AML and FLT-3-ITD AML cells were more vulnerable to SYK suppression than their FLT-3 wild-type (WT) counterparts. SYK overexpression was also found to promote resistance to FLT-3-ITD-targeted therapy in an in vivo FLT-3-ITD model of AML.

This study will evaluate the safety and efficacy of TAK-659 for the treatment of AML. The study is designed to assess the efficacy of TAK-659 in both FLT-3-ITD and FLT-3 WT patient populations. A retrospective analysis will also be performed to explore the contribution of FLT-3 and/or SYK inhibition to the level of clinical activity observed.

Rationale for Pharmacokinetic Assessments

In the AML Dose Escalation cohorts, blood will be collected during Cycle 1 using an intensive sampling schedule so as to permit the detailed characterization of the plasma pharmacokinetics (PK) of TAK-659. Specifically, serial plasma PK assessments will be used to characterize single- and repeat-dose concentration-time profiles of TAK-659, calculate PK parameters, evaluate the dose-exposure relationship, assess dose- and time-dependence of PK parameters, and contribute to the development of a population PK model for TAK-659. The PK sampling time points are derived from considerations of clinic practicality and patient convenience. Sampling will be conducted on Days 1, 2, 15, and 16 of Cycle 1 to allow evaluation of the accumulation of TAK-659 with QD or twice-daily (BID) dosing.

In the AML Dose Expansion cohorts, blood will be collected during Cycle 1 (on Days 1 and 15) to support population PK model development.

Plasma PK data collected in the AML Dose Escalation cohorts and the AML Dose Expansion cohorts may be used individually or in combination with data from other studies to explore the relationship between TAK-659 PK and pharmacodynamics effects, pharmacogenomics in drug metabolizing enzymes and/or transporters, electrocardiogram (ECG) parameters (eg, QTc), other safety parameters, and clinical response.

CCI

[redacted]

predictive of safety issues and/or clinical response to TAK-659, and/or that account for clinically meaningful variability in drug exposure.

1.5 Potential Risks and Benefits

Because TAK-659 has been administered to a total of only 181 patients as of 05 September 2017, it is not currently possible to describe with certainty the potential adverse effects of the compound.

1.5.1 Potential Risks From Nonclinical Studies

Potential risks from nonclinical studies in dogs and rats include the following:

- Lymphoid/hematopoietic effects that include lymphoid depletion and myelosuppression that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased susceptibility to infection, bleeding, and anemia.

- Epithelial effects on the intestinal tract, urinary tract, and lens. Intestinal effects included minimal-to-slight mucosal hemorrhaging. Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis that led to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.

- Reproductive system effects, including decreased spermatozoa and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries.

- Possible mutation of DNA.

- Growth plate thickening and disorganization (not relevant to adults).

- Lymphoid and hematopoietic effects and reproductive system effects are considered important potential risks.

1.5.2 Potential Risks From Clinical Studies

Potential risks based on clinical observations include the following:

On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated

at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, asymptomatic lipase or amylase elevations are reported commonly (≥10% of patients). Patients in Study C34002 will have frequent monitoring of lipase and amylase as outlined in the Schedule of Events.

Cases of pneumonitis have been reported in clinical studies with B-cell receptor (BCR) pathway kinase inhibitors, including TAK-659, and pneumonitis is considered an important potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

There have been occurrences of opportunistic infections such as PJP in some patients who had fever. These patients had other underlying conditions that made them prone to infections. With the limited experience we have with TAK-659, we have not determined whether TAK-659 is directly associated with the occurrences of these infections.

Further details regarding the benefits and risks associated with TAK-659 may be found in the current version of the TAK-659 IB.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are:

- Phase 1b dose finding phase: to determine the safety, tolerability, and MTD/ RP2D of TAK-659 administered orally on a QD or BID dosing schedule in patients with relapsed or refractory AML
- Phase 2 expansion phase: to evaluate preliminary efficacy of TAK-659 in relapsed or refractory AML as measured by overall response rate (ORR)

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate additional efficacy measures of TAK-659, such as duration of response (DOR), time to progression (TTP), mortality rate at 3 and 6 months, and overall survival (OS)

- To evaluate differential efficacy of TAK-659 in patients with or without FLT-3-ITD mutation

- To characterize the plasma PK of TAK-659 in patients with relapsed or refractory AML

2.3 Exploratory Objectives

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints are:

- Dose finding phase: AEs, serious adverse events (SAEs), dose-limiting toxicities (DLTs) (Cycle 1), clinical laboratory values, and vital sign measurements.

- Phase 2 dose expansion phase: ORR (which will include CR, CR with incomplete platelet recovery [CRp], CR with incomplete hematologic recovery [CRi], CR with partial hematologic recovery [CRh], a composite complete remission [CRc defined as the sum of patient achieving a CR, CRh, CRi, or CRp], and PR).

3.2 Secondary Endpoints

The secondary endpoints are:

- DOR.
- TTP.
- Mortality rate at 3 and 6 months.
- OS.
- ORR, DOR, TTP, mortality rate at 3 and 6 months, and OS in FLT-3-ITD mutant versus WT populations.
- Plasma PK parameters, including but not limited to maximum (peak) plasma concentration (C_{max}), first time to reach maximum (peak) plasma concentration (t_{max}), area under the plasma concentration versus time curve over the dosing interval (AUC_{τ}), apparent clearance (CL/F), accumulation ratio (Rac), and peak-trough ratio (PTR).

3.3 Exploratory Endpoints

CCI

4. STUDY DESIGN

4.1 Overview of Study Design

This study is an open-label, multicenter, phase 1b/2, dose escalation, and expansion study of TAK-659 in adult patients with relapsed or refractory AML. This study will include a phase 1b dose finding portion and single-arm phase 2 expansion portion. The patient population will consist of adults previously diagnosed with primary or secondary AML for whom no standard therapies are anticipated to result in a durable remission based on the opinion of the investigator, or who refuse standard therapies. For the phase 2 portion of the study, patients must be refractory to or relapsed after no more than 2 prior chemotherapy regimens.

It is expected that approximately 40 patients will be enrolled in the phase 1b portion and up to 66 patients will be enrolled in the phase 2 portion of this study. Once enrolled into the study, patients will be administered TAK-659 tablets (available in 20-, 60-, and 100-mg dosage strengths). Each 28-day treatment cycle will be composed of 28 consecutive days of QD or BID TAK-659 treatment. Patients, including those who achieve a CR, may receive TAK-659 until they experience disease progression.

The starting dose for the phase 1b portion of this study (Study C34002) will be directed by the current Study C34001, the FIH dose escalation study of TAK-659 in patients with advanced solid tumors and lymphoma. The starting dose in Study C34002 will not exceed the highest dose determined to be safe in Study C34001 at the time Study C34002 starts. A dose of 60 mg QD has been determined to be tolerable based on a 3+3 dose escalation schema after evaluation of 6 patients. Based on these data, the starting dose will be 60 mg QD for Study C34002. Since the initiation of Study C34002, dose escalation has been completed in Study C34001 with 100 mg QD determined as the MTD. In the expansion phase of the ongoing FIH study, lymphoma patients are being evaluated at 100 mg and early clinical activity has been observed in this population. In the NHL population, the more relevant target for TAK-659 is SYK.

To determine the MTD of TAK-659 in AML, an approach using a 3+3 dose escalation design will be used as detailed in Section 6.3. Planned dose escalation will follow 20-mg increments of escalation (eg, from 60 mg to 80 mg QD). A more aggressive dose escalation (more than 20-mg increments but not exceeding 100% escalation), evaluation of alternative dosing regimens (eg, BID), and expansion of an existing dose level up to 12 evaluable patients are all permissible following discussions between the sponsor and the investigators

if supported by evolving safety, tolerability, and PK data. Dose escalation will continue until either MTD is reached or the RP2D (if different from MTD) has been determined based on safety, tolerability, preliminary PK, PIA, and preliminary efficacy data, if available.

At least 6 patients will be evaluated at RP2D (either the MTD or at a lower dose as determined) before making a decision to advance to the phase 2 dose expansion phase. In the process of determining or refining RP2D, expansion of more than 1 dose level to at least 6 patients (up to a maximum of 12 evaluable patients per dose level) is permissible so that early signs of clinical activity can be assessed to a greater extent to assist dose selection.

The phase 2 expansion study in relapsed or refractory AML will be conducted using a Simon's 2-stage design (see Study Overview Diagram). The primary objective of the phase 2 portion of the study is to detect an efficacy signal that warrants further development of TAK-659 in AML. The primary measure of efficacy for the phase 2 portion will be the ORR, which will include CR, CRp, CRi, CRh, CRc, and PR. Nine and 15 response-evaluable patients will be enrolled initially in the FLT-3 WT and FLT-3 ITD/tyrosine kinase domain (TKD) mutant cohorts, respectively, during the first stage. Best response will be assessed by the end of Cycle 4 of TAK-659 treatment for the purpose of an interim analysis between Stage 1 and Stage 2. The FLT-3 WT and FLT-3 ITD/TKD mutant cohorts will proceed to the second stage if ≥2 and ≥6 patients respond to treatment (ORR), respectively. Other efficacy measures, such as DOR, TTP, and mortality rate will also be considered in the decision to expand the study to the second stage. If the FLT-3 WT and/or FLT-3 ITD/TKD mutant cohort(s) proceed(s) to the second stage, a further 14 and 17 evaluable patients, respectively, will be assessed in the 2 cohorts.

Best responses from both cohorts will be assessed individually and combined in an effort to understand the all-comer response rate. For patients with known FLT-3 mutational status based on local data, enrollment and cohort assignment could proceed using the local results. Upon enrollment, the FLT-3 mutational status will be verified using a sponsor-designated central testing laboratory. The central laboratory data will be used as the default result and cohort reassignment will occur in the case of discrepant central versus local test results. Prospective FLT-3 mutational testing will be performed prior to enrollment for patients for whom local data are not available.

CCI [redacted]

CCI

[redacted]

AEs will be assessed, and laboratory values, vital signs, and ECGs will be obtained to evaluate the safety and tolerability of TAK-659. 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 [9]. Dose-limiting toxicities (DLTs) are defined in Section 6.2.

Patients will be treated until either disease progression or occurrence of unacceptable study drug-related toxicities. Patients may discontinue therapy at any time. Patients will attend the End of Study (EOS) visit 28 days (+10 days) after receiving their last dose of study drug or before the start of subsequent anticancer therapy (other than hydroxyurea) if that occurs sooner.

Assessment of disease response will follow the criteria outlined in the Revised Recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [10].

Blood samples for determination of the plasma concentration of TAK-659 will be obtained from patients in the AML Dose Escalation cohorts and the AML Expansion cohorts. These samples will be obtained during Cycle 1 at the time points specified in the Schedule of Events.

A plasma inhibitory assay [1] will be used to assess the FLT-3 and possibly SYK inhibitory effects of TAK-659 in vitro using plasma samples collected from patients exposed to TAK-659 at different dose/exposure levels as indicated in the Schedule of Events.

CCI

[redacted]

Bone marrow biopsies and aspirates for disease response monitoring will be obtained as described in the Schedule of Events. Residual and/or designated samples from bone marrow biopsies and aspirates collected for disease assessment will also be used for analysis of biomarkers.

4.2 Number of Patients

For the phase 1b portion, approximately 40 patients will be enrolled in this study from approximately 6 study centers in the United States. For the phase 2 portion, up to 66 patients will be enrolled in this study from approximately 10 to 15 global sites. Enrollment is defined as time of initiation of the first dose of study drug.

Patients who are withdrawn from treatment during Cycle 1 for reasons other than toxicity during the phase 1b portion of the study will be replaced. Patients in the phase 2 portion of the study who are not evaluable for response will be replaced.

4.3 Duration of Study

Patients, including those who achieve a CR, may receive TAK-659 until they experience disease progression. Patients will discontinue treatment if they have an unacceptable TAK-659–related toxicity. The maximum duration of treatment, however, will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Patients will be followed for 28 days after the last dose of TAK-659 or to the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs. All patients, including those patients no longer on treatment, will be assessed for survival. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every month until death, loss to follow-up, or withdrawal of consent for further follow-up for up to 12 months after discontinuation of the study drug. In addition, information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who achieve CR but discontinue study treatment while still in remission, disease progression based upon available local data will also be collected during the survival follow-up period.

The final analyses for the clinical study report may be conducted after all patients enrolled in the study have had the opportunity to complete 4 cycles of treatment with TAK-659.

It is anticipated that this study will last for approximately 66 to 72 months, including 34 to 36 months in the phase 1b portion and 32 to 36 months in the phase 2 portion.

5. STUDY POPULATION

Patients will be males and females age 18 years or older with histopathologically documented primary or secondary AML (excluding acute promyelocytic leukemia) as defined by WHO criteria, for whom no standard therapies are anticipated to result in a durable remission based on the opinion of the investigator, or who refuses standard therapies (phase 1b and 2). For the phase 2 portion of the study, patients must be refractory to or relapsed after no more than 2 prior chemotherapy regimens. Patients must have adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients must not have clinically significant toxicity from prior chemotherapy, hematopoietic stem cell transplant (HSCT) within 60 days of the first dose of TAK-659, or clinically significant graft-versus-host disease requiring ongoing immunosuppressive therapy.

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Patients must have a histopathologically documented diagnosis of primary or secondary AML (excluding acute promyelocytic leukemia), as defined by WHO criteria (Jaffe et al, 2001), for whom no standard therapies are anticipated to result in a durable remission according to the clinical judgement of the principal investigator, or who refuses standard therapies (phase 1b and 2).

3. Patients for the phase 2 portion of the study must, in addition, meet the following:

    a. Patients must be refractory to or relapsed after no more than 2 prior chemotherapy regimens. Re-induction with the same regimen or stem cell transplant will not be considered a separate regimen.

4. Eastern Cooperative Oncology Group performance status of 0 to 1 (refer to Section 14.2).

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 1 highly effective method of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing the informed consent through 180 days 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], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 180 days 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], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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. In the absence of rapid progressive disease, the interval from prior systemic anticancer treatment to time of TAK-659 administration should be at least 2 weeks for cytotoxic agents (other than hydroxyurea), or at least 5 half-lives for noncytotoxic agents, and patients have to have recovered from acute toxicities of these therapies. Patients who are on hydroxyurea may be included in the study and may continue on hydroxyurea for the first 28 days while participating in this study.

8. Suitable venous access for the study-required blood sampling, including PK sampling and blood transfusion support.

9. Clinical laboratory values as specified in the following:

   - Total bilirubin must be ≤1.5 × the upper limit of normal (ULN).
   - Serum ALT and AST must be ≤2.5 × the ULN.
   - Lipase ≤1.5 × ULN and amylase ≤1.5 × ULN with no clinical symptoms suggestive of pancreatitis or cholecystitis.
   - Creatinine clearance ≥60 mL/min either as estimated by the Cockcroft-Gault equation (See Section 14.3) or based on urine collection (12 or 24 hours).

5.2 Exclusion Criteria

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

1. Clinically active central nervous system leukemia.

2. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

3. Any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially jeopardize the safety of the patient or interfere with the objectives of the study.

4. Systemic anticancer treatment (including investigational agents) ≤21 days or ≤5 × their half-lives before the first dose of study treatment. (For example, if the 5 × the half-life is shorter than 21 days, 5 × half-life should be used as the washout period. However, a minimum of 10 days should elapse from prior therapy to initiating protocol therapy.)

5. Persistent clinically significant toxicity from prior chemotherapy that is Grade 2 or higher by the NCI CTCAE (v4.03).

6. Receipt of HSCT within 60 days of the first dose of TAK-659; clinically significant graft-versus-host disease (GVHD) requiring ongoing immunosuppressive therapy

post HSCT at the time of screening (use of topical steroids for ongoing skin GVHD is permitted).

7. Active, systemic infection requiring intravenous (IV) antibiotic, antifungal, or antiviral therapy or other serious infection within 14 days before the first dose of study drug.

8. Major surgery within 14 days before the first dose of study drug and have not recovered fully from any complications from surgery.

9. Radiotherapy less than 2 weeks before the first dose of study treatment or have not recovered from acute toxic effects from radiotherapy.

10. Known human immunodeficiency virus (HIV) positive (testing not required).

11. Known hepatitis B surface antigen-positive, known or suspected active hepatitis C infection (testing not required).

12. Any of the following cardiovascular conditions:

    a) Acute myocardial infarction within 6 months before starting study drug;

    b) Current history of New York Heart Association (NYHA) Class III or IV heart failure (see Section 14.4);

    c) Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities;

    d) Fridericia's corrected QT interval (QTcF) > 450 milliseconds (msec) (males) or > 475 msec (females) on a 12-lead ECG during the Screening period;

    e) Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant.

13. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-659 including difficulty swallowing tablets; diarrhea > Grade 1 despite supportive therapy.

14. Use or consumption of any of the following substances:

    a) Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, the use of these agents is not permitted during the study except for AE management (see Section 6.7 for details). See Appendix 14.5 for a nonexhaustive list of strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the US Food and Drug Administration (FDA) Draft DDI Guidance.

    b) Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drug. In general, the use of these agents is not permitted during the study except for AE management (see Section 6.7 for details). See Appendix 14.5 for a nonexhaustive list of strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the US FDA Draft DDI Guidance.

    c) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are not permitted during the study.

15. White blood cell count > 50,000/μL; hydroxyurea may be used to control the level of circulating leukemic blast cell counts prior to study entry and, if needed, concomitantly while on TAK-659 treatment during the first 28 days of the study. Hydroxyurea can be used up to a maximum dose of 5 g/day.

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 subinvestigator(s).

The study drug will be dosed continuously, QD or BID, in 28-day cycles. The study drug should be taken on an empty stomach, at least 1 hour before and no sooner than 2 hours after

ingestion of food and/or beverages other than water. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed dose. Patients should swallow the study medication whole. The study medication should not be chewed, crushed, or manipulated in any way before swallowing. Administration of the tablets will be guided by the dosing tables included in the Pharmacy Manual.

Patients should be instructed to take their study medication at approximately the same time each day and to not take more than the prescribed dose at any time. On visit days, patients should be instructed to hold their dose until predose assessments are performed. For BID dosing, morning and evening doses should be approximately 12 hours apart. In the event that a patient fails to take the TAK-659 dose at their scheduled dosing time (±6 hours of their scheduled dosing time for QD dosing; ±3 hours of their scheduled dosing time for BID dosing), that dose should be skipped and the patient must not make dose adjustments on that day or subsequent days to account for the missed dose, for example, by taking a double dose of TAK-659 on the following day. Patients should record any skipped doses in their dosing diary (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after study medication ingestion, patients should not re-dose following emesis and should record the time of the emesis in their dosing diary (see the Study Manual). Patients should resume dosing at the next scheduled time with the prescribed dosage.

6.2 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010 [9]. 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 TAK-659:

- Prolonged myelosuppression with the persistence of ≥Grade 4 neutropenia or ≥Grade 4 thrombocytopenia in the absence of leukemia (blast count <5% in bone marrow) at least 42 days after the initiation of Cycle 1 therapy

- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Grade 3 nausea and/or emesis resolved to ≤ Grade 1 or baseline in a week after the use of an optimal antiemetic regimen based on standard practice. The optimal antiemetic regimen is defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor ($5\text{-}HT_3$) antagonist and a corticosteroid given in standard doses and according to standard schedules.
    - Grade 3 diarrhea that resolved to ≤ Grade 1 or baseline in a week after receiving the maximal supportive therapy based on standard practice.
    - Brief (<1 week) Grade 3 fatigue.
    - Asymptomatic Grade 3 laboratory abnormalities that are considered to be not clinically significant. The determination of the clinical significance will be made jointly by the investigators and the sponsor and documented in writing.
- Failure to administer ≥75% of planned doses of the study drug due to TAK-659–related or possibly related hematological (considered not related to leukemic infiltration) or nonhematologic toxicities.
- Other TAK-659–related Grade 2 or greater nonhematologic toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with TAK-659.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

6.3 Dose Escalation Rules

A 3+3 dose escalation design will be used to determine the MTD of TAK‑659 in AML. The starting dose for the dose escalation portion of this study (Study C34002) will be directed by the current Study C34001, the FIH dose escalation study of TAK-659 in patients with advanced solid tumors and lymphoma. The starting dose in Study C34002 will not exceed the highest dose evaluated to be safe in Study C34001. A dose of 60 mg QD has been determined to be safe and tolerable based on the 3+3 dose escalation schema after evaluation of 6 patients. Based on these data, the starting dose will be 60 mg QD for Study

C34002 unless additional data from Study C34001 indicate a higher dose is safe. Since the initiation of Study C34002, dose escalation has been completed in Study C34001 with 100 mg QD determined as the MTD.

Planned dose escalation will follow 20-mg increments of escalation (eg, from 60 mg to 80 mg QD). A more aggressive dose escalation (more than 20-mg increments but not exceeding 100% escalation), evaluation of alternative regimens (e.g. BID), and expansion of an existing dose level up to 12 evaluable patients are all permissible following discussions between the sponsor and the investigators, if supported by evolving safety, tolerability, and PK data of TAK-659. Dose escalation will continue until either MTD is reached or the RP2D, if different from MTD, has been determined based on safety, tolerability, preliminary PK, and preliminary efficacy data, if available.

The dose escalation plan, as specified in Table 6-1, is based on the starting dose of 60-mg TAK-659 QD, the dose thus far determined to be tolerable in Study C34001. Escalation will be based on safety as determined in Cycle 1. While the primary escalation schema is designed to determine a classical Cycle 1-based MTD, dose escalation may be halted at any time after consultation between the sponsor and investigators if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable RP2D. At least 6 patients will be evaluated at the MTD or RP2D before making a decision to advance to phase 2 dose expansion. In the process of determining or refining RP2D, expansion of more than 1 dose level to at least 6 patients (up to a maximum of 12 evaluable patients per dose level) is permissible so that pharmacodynamic measures and early sign of clinical activity can be assessed to a greater extent to assist dose selection.

Escalation rules based on DLTs include:

1. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level at which 3 patients will be enrolled.

2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.

3. Escalation will continue if 1 of 6 patients experiences DLT.

4. If 2 or more patients in any dose level experience DLT, enrollment at that dose level will stop. Following consultation between the sponsor and investigators, either the previous dose level will be considered the MTD (if 6 or more patients have been

studied at that dose level), the previous dose level will be expanded (if fewer than 6 patients have been studied at that dose level), or a dose level intermediate between the current and the previous dose level will be evaluated.

Figure 6-1 is a diagrammatic representation of these rules.

Figure 6-1 Dose Escalation Algorithm

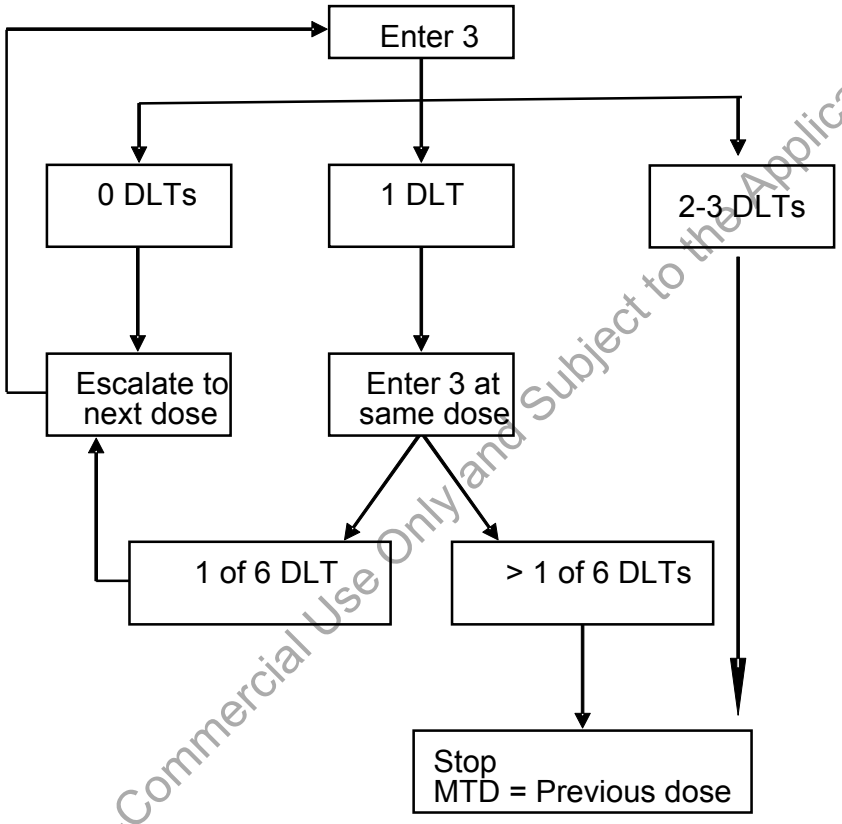


Table 6-1 Planned Dose Levels

Dose Level	Dose (unit)
Starting dose not exceeding highest safe dose evaluated in Study C34001:	
-2	20 mg
-1	40 mg
1	60 mg
2	80 mg
3	100 mg[a]

a Alternative dose escalation, including changing escalation increments, evaluation of alternative regimens/schedules (e.g. BID), and expansion of existing dose levels up to 12 evaluable patients, is permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for adjustment based on evolving safety, tolerability, and PK data.

DLT-evaluable patients in each dose cohort will consist of patients who have met the minimal treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met, if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1) and observed for ≥28 days following the dose on Cycle 1, Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude a DLT did not occur. Patients who do not meet these minimum requirements will be regarded as ineligible for inclusion as DLT-evaluable patients for the given dose cohort and may be replaced within the same cohort.

6.4 Dose Modification Guidelines

6.4.1 General Principles

Treatment cycles with TAK-659 are 28 days. The patient will be evaluated weekly during Cycle 1, every other week during Cycles 2 to 4, and then every cycle thereafter for possible toxicities that may have occurred after previous doses. Toxicities are to be assessed according to the NCI CTCAE, version 4.03. All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-659 may continue study treatment and maintain the same dose, or have doses of TAK-659 held or reduced, or permanently discontinue from the study. Detailed dose modification guidelines are provided in Sections 6.4.4 and 6.4.5.

Patients who have the TAK-659 dose held due to treatment-related or possibly related AEs may resume study drug after resolution of the AE, but may either maintain the same dose level or have doses of TAK-659 reduced (dose reduction) by at least 1 dose level. When a dose reduction occurs, the TAK-659 dose will be reduced to the next lower dose that either has been established as a safe dose during dose escalation, or is lower by a 20-mg increment (Table 6-1). If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 can be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of TAK-659. When a dose reduction of TAK-659 is required due to toxicity, no dose re-escalation will be permitted.

If TAK-659 dosing is delayed for > 21 days for TAK-659–related or possibly related toxicities despite supportive treatment per standard clinical practice or more than 2 dose reductions are required in a patient, this patient should be considered to have study treatment discontinued, unless the treating physician considers that the patient may benefit from continued study treatment after resolution of AEs to ≤ Grade 1, or baseline, or a level considered acceptable by the physician. The patient will continue to be followed for 28 days for safety evaluation after the last administration of TAK-659.

Patients who experience a DLT (during escalation) or DLT-like toxicity (during phase 2 of the study) during the first cycle will, in general, require that treatment with TAK-659 be permanently discontinued. If, in the opinion of the investigator and the sponsor (project clinician or designee), it is in the patient's best interest to continue treatment with TAK-659, then the dose of TAK-659 will be reduced by at least 1 dose level when treatment resumes after recovery of the toxicity or toxicities in question to ≤ Grade 1 or to baseline values or to a level considered acceptable by the investigator. This discussion will be documented in the study file. However, if a patient requires a dose delay of > 21 days for such an event to resolve despite the best supportive care permissible per protocol, then the patient must be discontinued from the study. The patient will be followed until resolution or stabilization of the event.

For management of toxicities on study, dose modification guidelines should be closely followed. However, based on evolving safety data of TAK-659 and/or individual patient cases, alternative dose modifications may be recommended after discussion between the investigator and the sponsor to maximize exposure of study treatment while protecting patient safety.

6.4.2 Intrapatient Dose Escalation

Intrapatient dose escalation is not allowed in this protocol.

6.4.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

TAK-659 is administered in continuous cycles; therefore, study drug should be administered continuously unless AEs occur that meet the dose modification criteria as outlined in the following.

6.4.4 TAK-659 Dose Modification for Hematologic Toxicities

Blood counts should be regularly monitored during the study as specified in the Schedule of Events, and tested more frequently if clinically indicated based on local standard practice. Comparison to baseline values and AE grading based on CTCAE (v.4.03) will be performed. When severe hematological AEs occur (≥Grade 4 events, febrile neutropenia, neutropenic infection, thrombocytopenia with signs of overt bleeding or clinically significant bleeding), close monitoring and medical management using supportive care if indicated will be given based on standard practice (See Section 6.7) while the study drug should be continued. If these events persist despite supportive care (not resolved to ≤Grade 1, or baseline, or a level considered acceptable by the investigator within 7 days), at the investigator's discretion, bone marrow aspirate assessment will be performed to evaluate whether the prolonged myelosuppression is due to leukemic infiltration or disease progression. If leukemic blasts are ≤5% in bone marrow and bone marrow aplasia is seen, the study drug should be continued for an additional 14 days with repeat bone marrow aspirate in the absence of peripheral hematologic recovery to assess marrow cellularity. In the absence of evidence for bone marrow recovery, the study drug should be withheld for up to 21 days.

Clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until recovery to ≤Grade 1 or baseline or a level considered acceptable by the investigator. Upon recovery, TAK-659 may be reinitiated either at the same dose level or at a reduced dose level at the discretion of the investigator. If no recovery occurs within 21 days (based on peripheral blood counts and/or repeat bone marrow aspirate) after the study drug hold (42 days in total after the first dose on Cycle 1, Day 1), the patient should discontinue study treatment, and if this occurs in Cycle 1, the patient will be considered to have had a DLT. The patient will continue to be followed until resolution or stabilization of the event,

initiation of another anti-leukemia therapy, or overt AML progression, whichever occurs first.

Based on each individual patient's case, if according to the opinion of the investigator, an alternative dose management plan should be considered in the best interest of the patient, deviation from this general dose modification and discontinuation guideline is permissible upon discussion between the investigator and the sponsor.

When a dose reduction of TAK-659 is required, no re-escalation of dose will be permitted.

6.4.5 TAK-659 Dose Modification for Nonhematologic Toxicities

Please refer to Table 6-2 for dose held and dose reduction recommendations for nonhematologic toxicities. When the dose of TAK-659 is withheld based on the following criteria (Table 6-2), clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to ≤Grade 1, or baseline, or a level considered acceptable by the investigator (must be ≤Grade 2). Upon recovery, TAK-659 may be reinitiated either at the same dose level or at a reduced dose level. For events in which there are transient lab value abnormalities that, based on investigator assessment, are not clinically significant or related to disease and not the drug, continuation of therapy without following the dose modification guideline is permissible upon discussion with the sponsor.

Table 6-2 TAK-659 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 1 week with optimal antiemetics and antidiarrheal following standard of care • Transient Grade 3 fatigue (lasting <1 week) • Asymptomatic lipase elevation (<Grade 4) in the absence of significant amylase elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators • Asymptomatic amylase elevation (<Grade 4) in the absence of lipase elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators • Grade 3 hypophosphatemia resolved to Grade ≤1 or baseline within 72 hours with phosphate repletion • Other asymptomatic Grade 3 laboratory abnormalities that are considered to be not clinically significant, as determined jointly by the investigators and the sponsor	Hold TAK-659 until resolution to ≤Grade 1 or baseline or a level considered acceptable by the investigator (must be ≤Grade 2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurrence occurs, then reduce dose by 1 dose level. For the exceptions listed, maintain the dose level (no dose hold required). Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 21 days despite temporary disruption of study drug.
Grade 4 nonhematologic toxicities with the exception of: • Asymptomatic Grade 4 lipase elevation in the absence of significant amylase elevation (<Grade 3). • Asymptomatic Grade 4 amylase elevation in the absence of significant lipase elevation (<Grade 3). • Asymptomatic Grade 4 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3). • Grade 4 hypophosphatemia resolved to ≤Grade 1 or baseline value within 72 hours with phosphate repletion. • Other Grade 4 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigator.	Consider permanently discontinuing TAK-659, except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. Dose reduction of ≥1 dose level is required if study treatment resumes after resolution to ≤Grade 1 or baseline values. For the exceptions, hold TAK-659 until resolution to ≤Grade 1 or baseline values or to a level that is clinically acceptable as determined by Investigator (≤Grade 2), then: • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level. • If recurrence occurs, then reduce dose by 1 dose level.

Grade 4 nonhematologic toxicities will, in general, require that treatment with TAK-659 be permanently discontinued. If, in the opinion of the investigator and the sponsor (project clinician or designee), it is in the patient's best interest to continue treatment with TAK-659, then the dose of TAK-659 will be reduced by at least 1 dose level when treatment resumes after recovery of the toxicity or toxicities in question to ≤ Grade 1or to baseline values or to a level considered acceptable by the investigator (must be ≤ Grade 2). When a dose reduction of TAK-659 is required, no re-escalation of dose will be permitted.

Based on each individual patient's case, if according to the opinion of the investigator, an alternative dose management plan is considered in the best interest of the patient, deviation from this general dose modification and discontinuation guideline is permissible upon discussion between the investigator and the sponsor.

6.5 Concomitant Medications and Procedures

During the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is taking or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the informed consent form (ICF) through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

The following restrictions apply during the study:

- Any antineoplastic therapy other than TAK-659 (with the exception of hydroxyurea for the first 28 days of study drug treatment). This includes chronic use of corticosteroids at daily doses greater than the equivalent of 10 mg of prednisone as part of any anticancer treatment regimens. If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).

- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) in Cycle 1 during dose escalation. Patients who experience severe and/or febrile neutropenia can be managed with growth factor support if needed in accordance with American Society of Clinical Oncology (ASCO) guidelines.

- Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A should be avoided in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix 14.5 for a nonexhaustive list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA draft guidance for DDI studies.

- Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
- Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone
- Antidepressant: nefazadone
- Immunosuppressant: cyclosporine
- Calcium channel blockers: diltiazem, felodipine, mibefradil, verampamil
- Antiarrhythmics: amiodarone, dronedarone, quinidine
- Antiplatelet: ticagrelor
- Antilipid: avasimibe
- Other cardiovascular: captopril, carvedilol, ranolazine
- Vasopressin antagonist: conivaptan
- Food/Herbals/Supplements: grapefruit-containing food and beverages, St. John's wort, quercetin

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and Appendix 14.5 may be used for AE management if there is no appropriate alternative treatment available per the investigator's judgment. This situation will be handled on a case by case basis, and requires discussion between the investigator and the medical monitor to assess the relative benefit and risk for a

given patient. The discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

Note that medications used to treat HIV or hepatitis C infection are not listed above or in Appendix 14.5 because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a or P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list above or in Appendix 14.5, then its use must be discussed on a case-by-case basis with the medical monitor or designee to assess the relative benefit and risk. The discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

6.6 Precautions and Restrictions

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-659 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. Nonsterilized 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 1 highly effective method of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing of the ICF through 180 days 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], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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 180 days 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], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

6.7 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as blood products (red blood cell [RBC] and platelet transfusions), antiemetics, and pain medications are permitted as needed per American Society of Hematology (ASH)/ASCO guidelines or local institutional practice. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation.

Pneumonitis

Patients with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis after ruling out infectious causes and alternative etiologies. If pneumonitis is suspected, TAK-659 treatment should be interrupted and the patient treated per standard of care. If pneumonitis is moderate/severe, discontinue TAK-659. Patients should be monitored for respiratory signs and symptoms throughout treatment and be advised to promptly report respiratory symptoms.

Nausea and/or Vomiting

This study allows prophylactic use of antiemetics as clinically indicated before dosing with the study drug. Premedication with oral ondansetron as monotherapy administered without steroids is recommended. However, different practices may be followed if they are based on institutional standard of care. In addition, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. An optimal antiemetic regimen is defined as one that employs both 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

Diarrhea

Prophylactic antidiarrheals will not be used in this protocol before the first dose of study drug. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Edema (Including Periorbital)

Peripheral and periorbital oedema have been observed in patients treated with TAK-659. Management of the event, if it occurs, should follow the standard local practice and dose modification should proceed following the dose modification guideline in Table 6-2.

Anemia

Hemoglobin should be monitored regularly as outlined in the Schedule of Events, with additional testing obtained according to standard clinical practice. Packed RBC transfusion is permitted, as necessary, per local institutional practice. In general, RBC transfusion is recommended for all symptomatic patients with anemia or any asymptomatic patients with a hemoglobin ≤ 7 to 8 g/dL with the purpose of maintaining the hemoglobin between 8 and 10 g/dL depending on patients' age, symptoms, and comorbid conditions. Each transfusion episode, including the type of transfusion (RBC), should be recorded. Erythropoietic agent use at the investigator's discretion is also allowed and should be administered according to institutional practice.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the Schedule of Events with additional testing obtained according to standard clinical practice. Platelet transfusion is

allowed to manage severe thrombocytopenia to prevent and minimize bleeding according to ASH/ASCO guidelines. In general, platelet transfusion should be given prophylactically to patients with platelet counts < 10,000/μL or to any patients with signs of overt bleeding, such as oral purpura. Each transfusion episode, including the type of transfusion (platelets), should be recorded.

Neutropenia

Blood counts should be monitored regularly as outlined in the Schedule of Events with additional testing obtained according to standard clinical practice. Myeloid growth factors (eg, G-CSF, GM-CSF) may be used to treat severe and/or febrile neutropenia according to ASCO guidelines. However, it should be noted that growth factors are not used routinely in AML patients undergoing chemotherapy, and prophylactic use of myeloid growth factors should be avoided during the first cycle of dose escalation (See Section 6.5).

Prophylaxis Against Infection

The severe and prolonged period of neutropenia seen with therapy is frequently associated with neutropenic fevers and a high risk of infection with bacteria or fungi and viral reactivation. To minimize the risk of infection, it is recommended that patients be placed on "neutropenic precaution", with or without the addition of prophylactic antibiotics, antifungals, or antivirals. In addition, patients should be screened for possible infectious foci (eg, dental status).

The components of "neutropenic precaution" may vary by institution but most commonly include: a high efficiency particulate air-filtered room, a diet free of raw berries or vegetables grown in dirt, no sick visitors, and no smoking. In addition, hand washing by all visitors and caregivers should be strictly enforced.

Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the patient is more prone to developing neutropenia; however, the use of such agents should be at the discretion of investigators based on the local standard practice. Patients who develop neutropenic fever should be evaluated promptly and treated immediately with parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.

Patients with lymphopenia and neutropenia may be more prone to developing infections, such as respiratory tract infections or pneumonia. Consider a diagnosis of opportunistic

infection including PJP in patients presenting with shortness of breath, cough, or fever. Prophylaxis for PJP may be initiated (either at baseline or during treatment) if clinically indicated. For older patients, patients with recent exposure to steroids or immunosuppressive agents, or patients who, in the investigator's opinion, are more susceptible to opportunistic infection at baseline, PJP prophylaxis should be considered at the start of the study treatment. When steroids and/or any immunomodulatory agents need to be used to manage the AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is coadministered. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated. However, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

Myelosuppression can also be associated with reactivation of herpes zoster, CMV, herpes simplex and other viruses. Antiviral therapy such as acyclovir, gancyclovir, valacyclovir, or other antiviral agents may be initiated as clinically indicated. Testing of CMV replication by a local polymerase chain reaction (PCR) assay will be required at baseline, and further monitoring and prophylactic or preemptive therapy to asymptomatic patients, if indicated, should follow the institutional standard practice. The following agents should be considered for prophylaxis or preemptive treatment against CMV: ganciclovir intravenously (IV), valganciclovir (orally), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until CMV is no longer detected by PCR.

Leukocytosis

For patients who develop symptoms of leukocytosis (WBC > 100,000/mm^3) while on the study, TAK-659 treatment should be withheld until the leukocytosis symptoms are controlled. Treatment of leukocytosis symptoms may include leukapheresis and hydroxyurea administration (concurrent use of hydroxyurea with the study drug is only permitted during the first 28 days of study treatment) per institutional guidelines. When the WBC of the patient is < 50,000/mm^3 and symptoms are improved, TAK-659 treatment may be restarted after consulting with the project clinician.

Fluid Deficit

Fluid deficit should be corrected before initiation of study drug and during treatment.

Rash With or Without Pruritus

Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of

a topical or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Treatment with TAK-659 must be withheld in the event of Grade 3 or 4 rash. Refer to dose modification guideline in Table 6-2.

Hypophosphatemia

Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise refer to dose modification guideline in Table 6-2.

Enzyme Elevations

Transaminase, Amylase and Lipase, and CPK Elevations

Elevations of the enzymes above have been observed. Events are generally asymptomatic and reversible with dose interruption. See dose modification guideline in Table 6-2.

Lactate Dehydrogenase Elevations

Lactate dehydrogenase (LDH) elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic and the clinical significance is unknown. No doses have been interrupted due to increased LDH; however, LDH elevations have been observed to be reversible in patients who had TAK-659 interrupted due to other reasons.

6.8 Blinding and Unblinding

This is an open-label study.

6.9 Description of Investigational Agents

TAK-659 has been formulated into immediate-release film-coated tablets for use in clinical studies via a common granulation process. Three different tablet dosage strengths, 20, 60, and 100 mg, were formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets were coated with Opadry® film coat.

6.10 Preparation, Reconstitution, and Dispensation

Detailed instructions for the dispensing of TAK-659 immediate-release film-coated tablets are provided in the Pharmacy Manual.

TAK-659 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-659.

6.11 Packaging and Labeling

TAK-659 20-, 60- and 100-mg tablets will be packaged into round, white, high-density polyethylene (HDPE) bottles with induction seal, desiccant pack, and polypropylene child-resistant caps. Each bottle of TAK-659 will be labeled with either a single-panel or multilanguage label containing pertinent study information, country-specific requirements, and a caution statement.

6.12 Storage, Handling, and Accountability

TAK-659 tablets should be stored in the original dispensing bottles at room temperature of 1°C to 25°C (33.8°F to 77°F). Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients, returned to sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies received at the clinical sites will be counted and reconciled before being returned to the sponsor.

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 project clinician for this study, the central laboratory and any additional clinical laboratories, the contract research organization (CRO) team, and other vendors may be found in the Study Manual. A full list of investigators is available in the sponsor's or CRO'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 study that incorporates a phase 1b dose escalation and a phase 2 dose expansion at the MTD and/or RP2D. In the Dose Escalation phase, AML patients will be assigned a

cohort based on the dose escalation rules described in Section 6.3. In the dose expansion phase, AML patients will be assigned to a cohort as described in Section 4.1. All patients will receive TAK-659.

7.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and End of Study (EOS). Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Procedures conducted during the Screening period that are performed within 3 days of Cycle 1, Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified.

Unless otherwise noted, evaluations during the Treatment period must occur before study drug administration at scheduled visits. Tests and procedures should be performed on schedule for all visits. The timing of PK and plasma inhibitory assay assessments is specified in the Schedule of Events and is not flexible. Other laboratory assessments and procedures may occur within -3 days before the scheduled day, and Day 1 of Cycle 2 and beyond may be modified by up to 3 days due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).

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 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 7.4.9. Sites will be required to record any screening reports

on tumor cytogenetics and/or mutation assays (eg, FLT-3) performed as part of the standard of care.

7.4.4 Physical Examination

A physical examination (PE) will be completed per standard of care at the times specified in the Schedule of Events. During dose escalation, complete PEs will be performed at screening, Day 1 of each cycle of treatment, and EOS. Symptom- or finding-directed PEs will be performed on Days 8, 15, and 22 of Cycle 1 and Day 15 of Cycles 2, 3, and 4. During the phase 2 expansion, complete PEs will be performed at screening only, and post screening PEs will be symptom or finding directed.

Note: Physical examinations at screening will include a neurological examination.

7.4.5 Patient Height and Weight

Height will be measured only during screening (within 28 days before the first dose of TAK-659).

Weight will be measured during the times specified in the Schedule of Events.

7.4.6 Vital Signs

Vital sign measurements include diastolic and systolic blood pressure, heart rate, and temperature, and will be assessed as specified in the Schedule of Events. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for approximately 5 minutes.

7.4.7 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status is to be assessed at the times specified in the Schedule of Events.

7.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. A urine pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose may be administered. If the serum pregnancy test is performed within 3 days from the first dose and the result is negative, the urine pregnancy test on Cycle 1, Day 1 may be waived.

7.4.9 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded in the eCRF from the time of the first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first. See Section 6.5 for a list of medications and therapies that should be avoided during the study unless otherwise specified.

7.4.10 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.

7.4.11 Enrollment

A patient is considered to be enrolled in the study when the first dose of TAK-659 has been administered.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.12 Electrocardiogram

12-lead ECGs will be performed and interpreted locally. ECGs will be obtained at the time points specified in the Schedule of Events. The ECG schedule is more intensive for patients enrolled in the dose escalation cohorts. The time points for ECG collection may be revised based on emerging PK data, but the number of time points will not increase.

Unless otherwise specified by the Schedule of Events, scheduled ECGs should be performed predose and after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK, PIA, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

Confirmation that the machine-estimates of the rate-corrected QT interval (milliseconds) of electrocardiograph (QTc) are accurate using the appropriate QT correction formula (QTcF, Bazett's corrected QT interval [QTcB]) should be performed. Estimates of QTc for study eligibility should use QTcF. In the event that a QTc value confirmed by the qualified reader is >475 msec, an evaluation to determine etiology should be conducted. If the prolonged

QTc finding can be corrected based on change in medication and/or correction of electrolyte abnormalities, and a repeat ECG meets eligibility requirements, the patient may enroll to the study upon review and agreement by the sponsor's clinician.

Following initiation of treatment, if a QTc value is confirmed by a qualified reader as > 500 msec for any ECG, the following will occur:

- The sponsor's clinician will be promptly notified.
- TAK-659 should be held and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).
- A formal consult by a cardiologist should be considered. Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.

The decision whether to reinitiate TAK-659 treatment with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc > 500 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated TAK-659, and appear to have benefited from TAK-659 treatment with either disease control or response will be agreed to by the investigator and the sponsor's clinician on a case-by-case basis.

The ECGs performed should be reviewed by the investigator or his/her delegate before the patient leaves the clinic on visit days.

7.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the Study and Laboratory Manuals. Clinical laboratory evaluations will be performed as outlined in the following:

Clinical Chemistry, Hematology, Urinalysis, and Virology

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])
- Percentage of leukemic blast cells

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- γ-Glutamyl transferase (GGT)
- Phosphate
- Albumin
- Alkaline phosphatase (ALP)
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium
- Amylase
- Lipase
- Total protein
- CPK

Urinalysis

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

When creatinine clearance is estimated, the Cockroft-Gault formula will be employed as follows (see Appendix 14.3):

$$Estimated\ creatinine\ clearance = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

Virology

- CMV

7.4.14 Ophthalmic Exam

A slit lamp eye examination will be performed by an ophthalmologist at screening; on Cycle 2, Day 1; on Cycle 7, Day 1; every 6 Cycles thereafter (±2 weeks); and at EOS. Based on the nonclinical toxicology findings with TAK-659 in rats, slit lamp examinations should focus on detecting any posttreatment changes in ocular lens. Examination and photographing of the retina will be performed at baseline but not during the study unless it is clinically indicated. Additional eye exams may also be performed, as required. Additionally, patients will be carefully monitored for eye complaints at each visit and instructed to report visual symptoms as soon as they occur.

7.4.15 Disease Assessment

Assessment of disease response will follow the criteria outlined in the Revised Recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [10]. Investigators are encouraged to consult the reference for more detailed explanation of response criteria.

CR, CRi, CRp, CRh, CRc, and PR are defined using the following criteria:

> **CR**: A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 1000/μL and platelets of ≥100,000/μL. A morphologic leukemia-free state requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods. The peripheral blood should have no leukemic blasts. Hemoglobin concentration or hematocrit has no bearing on remission status, although the patient must be independent of transfusions. There should be no residual evidence of extramedullary leukemia.
>
> **CRi (complete response with incomplete recovery of blood counts)**: After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (<1000/μL) or thrombocytopenia (<100,000/μL).
>
> **CRp (complete response without platelet recovery)**: CRp satisfies all CR criteria except platelets < 100,000/μL, but platelet transfusions are not necessary.

CRh (complete response with partial hematologic recovery): CRh is defined as no evidence of peripheral blasts and partial recovery of peripheral blast counts including ANC above 500/µL **and** platelets above 50,000/µL.

CRc: A composite **complete** remission is defined as the sum of patient achieving a CR, CRh, CRi, or CRp.

PR: This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Thus, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of ≤5% blasts may also be considered a PR if Auer rods are present.

Response assessments above generally follow the standard criteria except patients who achieve a CR, CRh, CRi, CRp, or PR are not required to be transfusion independent.

Progressive Disease

Because the IWG criteria for AML do not provide a standardized definition for progressive disease [10], in this protocol, progressive disease is defined as 1 of the following:

- >50% increase in bone marrow blasts from baseline value
- >50% increase in circulating blasts from baseline value with absolute blast count >1000/mm^3
- Development of biopsy-proven extramedullary disease, or new sites of extramedullary leukemia
  Note: If the initial marrow blast percentage is too high to base progression on a >50% increase in bone marrow blasts, then peripheral blood criteria will be used.

Investigators should note that some patients may benefit from continued treatment even though their bone marrow blast counts may fluctuate over the course of the first 4 cycles. These patients may experience transient increase in bone marrow blasts before demonstrating a significant blast reduction that meets response criteria as specified previously. **Therefore, patients may be allowed to remain on study, after discussion between the investigator and the project clinician, even if they meet the criteria for progressive disease based only on bone marrow blast counts**.

7.4.15.1 Bone Marrow Biopsy and Aspirate Collection and Analysis

Bone marrow biopsy and aspirate collection at screening will be required to assess disease burden, cytogenetics, karyotype, and cellular composition by flow cytometry. Additional bone marrow aspirates (remaining aspirate material from the first pull or a second or third pull of bone marrow aspirate) and biopsy specimens (segments of the first core biopsy or additional core biopsies) will also be required at screening for biomarker analysis (Section 7.4.16). During phase 1b dose escalation, if a patient has already had a bone marrow biopsy and aspirate performed within 28 days of Day 1 of Cycle 1, this procedure need not be repeated if results for disease assessment are available. If only one test (biopsy or aspirate) has already been performed within 28 days of Day 1 of Cycle 1, the site should discuss the case with the Millennium project clinician or delegate during eligibility determination.

However, during phase 2, bone marrow aspirate and biopsy is a screening (baseline) procedure needed for the purpose of enrollment into the trial for both disease assessment and biomarker studies. In particular, bone marrow aspirate is needed to confirm the FLT-3 mutation status in marrow blasts, and therefore essential for patient assignment to either the FLT-3-ITD or WT group. In cases for which the performance of this baseline procedure is difficult based on an individual patient's condition and a bone marrow aspirate/biopsy test has been performed within 28 days from Day 1 of Cycle 1, the site is encouraged to discuss the case with the Millennium project clinician or delegate. In this circumstance, the site is required to investigate whether adequate residual material from the last bone marrow aspirate/biopsy procedure remains available for collection and whether the tissue processing procedures for these remaining samples conform to the requirements of this trial for the purpose of biomarker evaluation. If so, these samples should be collected and sent to the Sponsor-designated laboratory(ies).

- Note that a bone marrow biopsy is required only at screening. However, post screening, a biopsy that allows more bone marrow tissue to be examined should be performed (eg, when spicules are absent from the aspirate sample or a dry tap occurs) per local institutional practice at the time of disease assessment.

In addition, bone marrow aspirate and/or biopsy specimens (if needed) will be collected to assess disease response between Days 22 and 28 at the end of Cycle 1, Cycle 2, and Cycle 4, provided that the disease assessment is available before Day 1 of the following cycle. Beyond Cycle 4, bone marrow aspirate and/or biopsy assessments (if needed) will be performed as clinically indicated based on changes in peripheral blood counts, or when it is needed to establish either CR or disease progression. At any of these time points, if adequate residual material remains, it should be sent to the Sponsor-designated laboratory(ies) for exploratory biomarker studies.

At the time of relapse in patients who have had initial response to TAK-659, bone marrow aspirates and/or biopsies will be collected for biomarker studies (Section 7.4.16).

- If a bone marrow aspirate and/or biopsy is performed per standard of care based on suspected progression, if adequate residual material remains, these samples should be sent to the Sponsor-designated laboratory(ies) after discussion with the sponsor to ensure the usability of the samples (whether conforming to the required tissue processing procedures for this study).

- If the patient has initially responded and subsequently shows clinical signs of relapse but a bone marrow aspirate and/or biopsy have not been obtained, the site will collect a bone marrow aspirate and/or biopsy at this time to assess disease. During the procedure, additional bone marrow aspirates (remaining aspirate material from the first pull or a second or third pull of bone marrow aspirate) and biopsy specimens (segments of the first core biopsy or additional core biopsies) will be collected for biomarker studies and sent to the Sponsor-designated laboratory(ies).

Details regarding the preparation, handling, and shipping of these samples are provided in the Laboratory Manual.

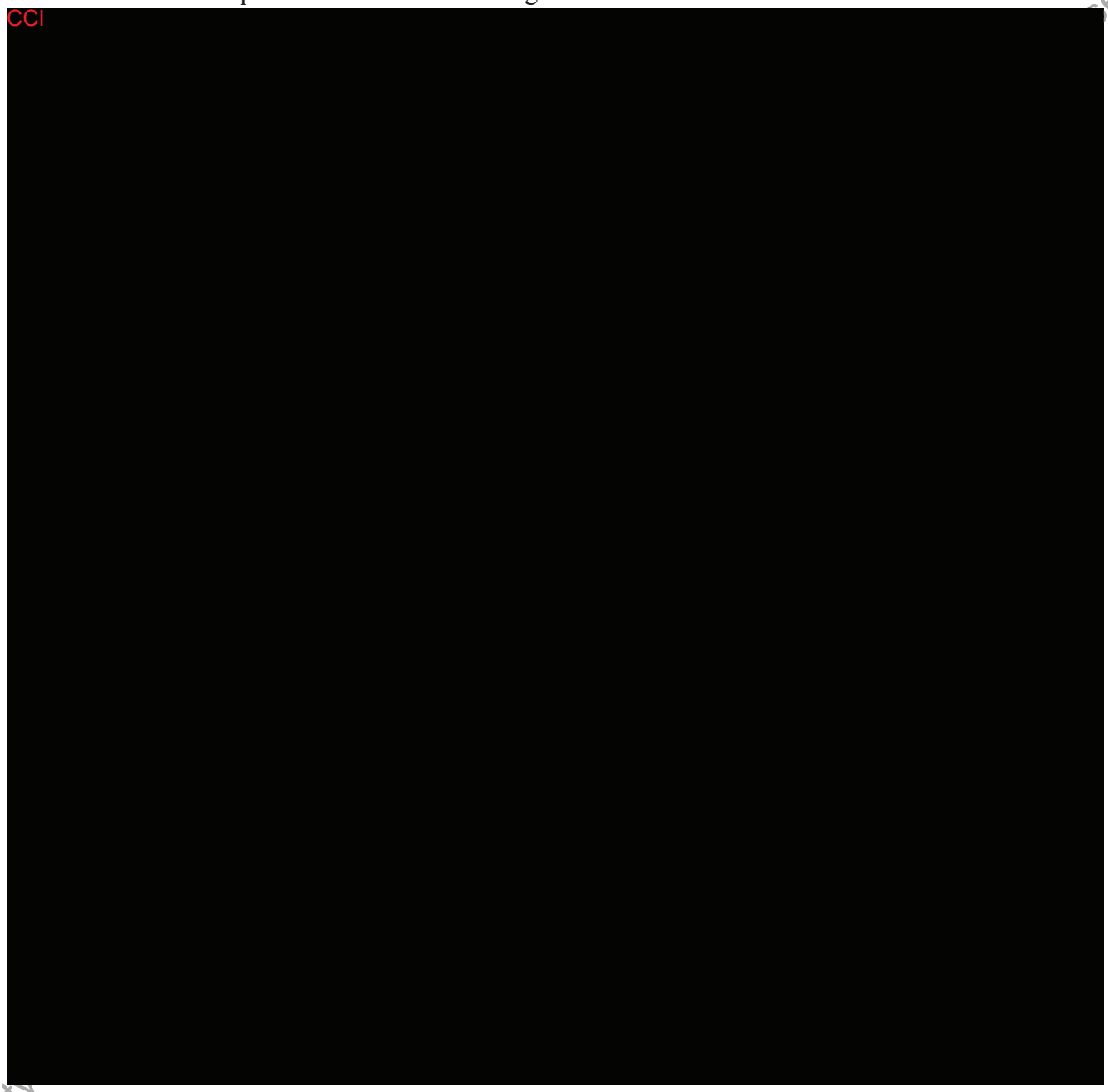
7.4.16 Biomarker Measurements

This study will investigate the biomarker hypotheses of both response and treatment-emergent resistance.

The following samples will be collected to facilitate these analyses:

- The FLT-3 mutation status will be confirmed using a blood sample and/or bone marrow aspirate collected at screening.

CCI



Sample shipping and handling instructions are provided in the Laboratory Manual.

Remaining samples from each of the collections listed may be used, if appropriate, to support other biomarker analyses described in this section. Based on the evolving data, it is at the sponsor's discretion to determine when and to what extent the biomarker studies

described in this section (except for the FLT-3 mutation assay) will be performed so that the patients' samples are used most appropriately in an attempt to generate informative data to the extent feasible.

7.4.17 Pharmacokinetic Measurements

The primary aim of PK sampling in this study is to measure the plasma concentrations of TAK-659. CCI [redacted]

Details on the collection, storage, processing, handling, and shipping of the PK samples are provided in the Laboratory Manual.

AML Dose Escalation Cohorts

Blood specimens for the determination of the plasma concentrations of TAK-659 will be obtained in Cycle 1 on Days 1, 2, 15, and 16. The specimens obtained on Days 2 and 16 should be obtained before the dosing of TAK-659 on those days (ie, they should be predose specimens). Blood sampling will be performed at the times indicated in the AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule. The timing but not the number of PK blood samples may be changed if emerging data indicate that an alteration in sampling scheme is needed to better characterize the PK of TAK-659.

AML Expansion Cohorts

Blood specimens for the determination of the plasma concentrations of TAK-659 will be obtained in Cycle 1 on Days 1 and 15. Blood sampling will be performed at the times indicated in the AML Dose Expansion (Phase 2) PK Schedule. The timing but not the number of PK blood samples may be changed if emerging data indicate that an alteration in sampling scheme is needed to better characterize the PK of TAK-659.

The remainder of the plasma PK samples from any sampling points in the expansion cohorts may be used to evaluate the FLT-3 and possibly SYK inhibitory effects of TAK-659 in vitro using a plasma inhibitory assay [1] (Section 7.4.16) if determined to be appropriate by the sponsor.

7.4.18 DNA Measurements

CCI [redacted]

CCI

[redacted]

7.4.19 Modified Charlson Comorbidity Index Assessment

Patients will be assessed during screening using the Modified Charlson Comorbidity Index (Section 14.1).

7.5 Completion of Treatment

A patient will be considered to have completed treatment if he/she discontinues treatment for any of the reasons outlined in Section 7.8.

7.6 Follow-Up Period

All patients, including those patients no longer on treatment, will be assessed for survival. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every month until death, loss to follow-up, or withdrawal of consent for further follow-up for up to 12 months after discontinuation of the study drug. In addition, information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who achieve CR but discontinue study treatment while still in remission, disease progression based upon available local data will also be collected during the survival follow-up period.

7.7 Completion of Study

Patients will be considered to have completed the study if:

- They are followed until death before the end of the survival follow-up window (up to 12 months after discontinuation of study drug for any reason)
- They remain on study treatment free of disease progression at the close of the study at least 1 year after their first dose of study treatment
- They continue on to the follow-up for survival after discontinuation of the study drug and reach the end of the 12-month OS follow-up window
- They discontinue study treatment while in CR and continue on to the follow-up for progression and either experience disease progression before the end of the 12-month follow-up period or reach the end of the follow-up period
- The sponsor terminates the study

7.8 Discontinuation of Treatment With Study Drug, and Patient Replacement

Patients may be allowed to remain on study, after discussion between the investigator and the project clinician, even if they meet the criteria for progressive disease based only on bone marrow blast counts.

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

- AE
- Protocol violation
- Progressive disease: as noted previously, patients with progressive disease may remain on study, after discussion between the investigator and the project clinician, if it is felt that they are deriving a clinical benefit from doing so.
- Symptomatic deterioration (at investigator's discretion)
- Unsatisfactory therapeutic response
- Initiation of hematopoietic stem cell transplant

- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

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

During the dose escalation phase, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced. During the expansion phase, patients who do not meet the response-evaluable criteria will be replaced.

7.9 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- AE.
- Protocol violation.
- Progressive disease.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

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.

7.10 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 be given a diary to record study drug dosing. The dosing diary will provide supporting information, if necessary. The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

Tests and procedures should be performed on schedule, but, unless otherwise specified, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. The timing of PK and plasma inhibitory assay assessments is specified in the Schedule of Events and is not flexible. If extenuating circumstances prevent a patient from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the patient may continue the study at the discretion of the investigator and after consultation with the Millennium clinician or designee.

If a dose of TAK-659 is held for up to 21 days for reasons unrelated to toxicity, the patient may be discontinued from the study following a discussion between the investigator and the sponsor.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

This study is noncomparative in nature, ie, formal statistical comparisons will not be performed. Summary tabulations will be presented that will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. A formal statistical analysis plan will be developed and finalized before database lock.

For the dose escalation cohort, statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed.

For the AML expansion cohort, ORR in the response-evaluable population will be tabulated descriptively with 95% exact binomial confidence intervals (CIs). Time-to-event data will be analyzed by the Kaplan-Meier method and results will be summarized by the 25th, 50th,

and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations, by FLT-3 WT and mutant populations.

8.1.1 Determination of Sample Size

During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 40 response-evaluable patients will be enrolled. The MTD/RP2D cohort will have at least 6 patients.

The sample sizes for the AML expansion cohort are estimated using a one-sided test at a significance level of $\alpha = 0.1$ with power of 80%. The FLT-3 WT cohort uses a null hypothesis of response rate ≤15%, versus an alternative hypothesis of response rate ≥35%. Based on a Simon 2-stage design and a 15% dropout rate, approximately 11 patients will be needed if the trial fails in the first stage, or 28 patients will be needed if the FLT-3 WT cohort succeeds in going to the second stage. The mutant cohort uses a null hypothesis of response rate ≤30%, versus an alternative hypothesis of response rate ≥50%. Based on a Simon 2-stage design and a 15% dropout rate, approximately 18 patients will be needed if the trial fails in the first stage, or 40 patients will be needed if the mutant cohort succeeds in going to the second stage.

8.1.2 Randomization and Stratification

For the dose escalation cohort, patients will be enrolled in successive dose cohorts. During the expansion, patients will be enrolled in 2 different cohorts based upon their FLT-3 mutation status as described in the Study Overview Diagram. 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 TAK-659 will be used for all safety analyses.
- Pharmacokinetic population: Patients in the AML Dose Escalation cohorts who have sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.

- Pharmacodynamics population: Patients with sufficient dosing in Cycle 1 and sufficient pharmacodynamics data derived from the Plasma Inhibitory Assay will be used for pharmacodynamics analyses.

- Response-evaluable population: Patients who receive at least 1 dose of study drug, have measurable disease at baseline, and 1 postbaseline disease assessment will be used for analyses of response.

- DLT-evaluable population: the DLT-evaluable population is defined as all patients in the phase 1b portion of the study who either experience DLT during Cycle 1 or complete at least 75% of the planned doses of TAK-659 and have sufficient follow-up data to allow the investigators and sponsor to determine whether a DLT occurred.

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. The relevance of missing sample data will be assessed.

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, body surface area (BSA), primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

Primary Efficacy

There is no primary efficacy endpoint for the dose escalation portion of the study. This study is not intended to demonstrate differences in treatment outcomes among disease groups. The primary endpoint for the AML expansion cohort is ORR. ORR is defined as the number of CRs and PRs in the response-evaluable population.

Secondary Efficacy

There is no secondary efficacy endpoint for the dose escalation portion of the study. The secondary efficacy endpoints for the AML expansion cohort are ORR in FLT-3 mutant and

FLT-3 WT populations, DOR, mortality rate at 3 and 6 months, and OS (by FLT-3 mutant cohort, FLT-3 WT cohort, and combined cohort). DOR is defined as the time from the date of first documentation of a response to the date of first documented progressive disease. OS is defined as the time from the date of study entry to death.

8.1.7 Pharmacokinetics/Pharmacogenomics/Biomarkers

Pharmacokinetic Analysis

The plasma concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay methods.

Plasma TAK-659 concentrations will be summarized by time postdose, grouped by dosing schedule, dose group, and dosing cycle and day. Mean and individual plasma TAK-659 concentration data will be plotted over time, grouped by dosing schedule, dose group, and dosing cycle and day.

Plasma PK data from the AML Dose Escalation cohorts will be used for the estimation of PK parameters in the PK-Evaluable Population. Standard single-dose (Cycle 1, Day 1) and multiple-dose (Cycle 1, Day 15) plasma PK parameters will be estimated using noncompartmental methods. Estimation of plasma PK parameters of the terminal disposition phase, such as terminal disposition phase half-life ($t_{1/2z}$) and area under the plasma concentration versus time curve from zero to infinity (AUC_{∞}) will depend on an adequate representation of the terminal disposition phase during the duration of PK sampling. Plasma PK parameters will be summarized, grouped by dosing schedule, dose group, and dosing cycle and day.

Dose proportionality of TAK-659 plasma exposures will be evaluated by visual inspection of plots of individual PK parameter values versus dose. If data permit, regression analysis using a power model will also be used to assess dose proportionality.

TAK-659 plasma concentration-time data collected in this study, together with data collected from other studies, may contribute to population PK analysis. If applicable, the specifics of the population PK modeling approaches will be described separately in a population PK analysis plan, and the results will be reported separately from the clinical study report.

CCI

[redacted]

8.1.8 Safety Analysis

Safety evaluations will be based on the incidence, intensity, and type of AEs; and clinically significant changes in the patient's vital signs, weight, and clinical laboratory results. Safety variables will be tabulated and presented for the safety population. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 28 days after the last dose of study drug, or until the start of subsequent antineoplastic therapy, whichever occurs first, will be tabulated. Treatment-emergent events will also include any AE that is considered by the investigator to be drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug related.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. AEs are to be tabulated using MedDRA system organ class, high-level term, and preferred term, and will include the following categories:

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

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients in the safety population) will be tabulated by the MedDRA preferred term.

Tabulation also will be provided that enumerates AEs by maximum intensity. Deaths, SAEs, and AEs resulting in study drug discontinuation will be tabulated. Clinical laboratory parameters will be summarized at each scheduled time point. Shift tables will be produced for selected laboratory parameters. These tables will summarize the number of patients with each baseline NCI CTCAE grade and changes to the worst NCI CTCAE grade during the study.

Descriptive statistics for the actual values of vital signs and weight over time will be tabulated by scheduled time point.

All concomitant medications collected from screening through the study period will be classified by preferred term according to the WHO drug dictionary.

Additional safety analyses may be determined at any time without prejudice to enumerate rates of toxicities and to further define the safety profile of study drugs.

Electrocardiogram Analysis

A summary of ECG abnormalities will be presented by visit. ECG intervals (QT, QTcB, QTcF, PR, QRS, and heart rate) will be summarized at each scheduled time point, along with change from baseline to each post treatment time point.

8.1.9 Interim Analysis

An interim analysis for futility stopping will be conducted to determine whether continuation of the AML expansion cohorts until study completion is warranted. The investigator-assessed response rate will be used as the endpoint for the interim analysis. The FLT-3 mutant and FLT-3 WT cohorts will be evaluated independently and could be subject to enrollment hold by individual cohort. For the FLT-3 mutant cohort, the interim analysis will be performed when the first 15 response-evaluable patients have had the opportunity to complete up to 4 cycles of therapy or have discontinued therapy before 4 cycles. If 6 or more responders are observed out of these initial 15 evaluable patients, patient enrollment will continue. The number of evaluable patients needed in the second stage is 17. For the FLT-3 WT cohort, the interim analysis will be performed when the first 9 response-evaluable patients have had the opportunity to complete up to 4 cycles of therapy or have discontinued therapy before 4 cycles. If 2 or more responders are observed out of these initial 9 evaluable patients, patient enrollment will continue. The number of evaluable patients needed in the second stage is 14.

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 [9]. 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 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
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1-202-315-3560
E-mail: takedaoncocases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial 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 [9]. 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 28 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 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 28 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 (CD) 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 PPD (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 Center	Phone	E-mail	Fax	Hours
CCI				Monday-Friday, 9 AM–7 PM, ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Cognizant (refer to 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 TAK-659 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 TAK-659 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 C34002 Amendment 02: An Open-Label, Phase 1b/2 Study Investigating Recommended Phase 2 Dose, Safety, Tolerability, and Preliminary Efficacy of TAK-659 in Adult Patients With Relapsed or Refractory AML

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. Levis M, Brown P, Smith BD, Stine A, Pham R, Stone R, et al. Plasma inhibitory activity (PIA): a pharmacodynamic assay reveals insights into the basis for cytotoxic response to FLT3 inhibitors. Blood 2006;108(10):3477-83.
2. Kuendgen A, Germing U. Emerging treatment strategies for acute myeloid leukemia (AML) in the elderly. Cancer Treatment Reviews 2009;35(2):97-120.
3. Laubach J, Rao AV. Current and emerging strategies for the management of acute myeloid leukemia in the elderly. Oncologist 2008;13(10):1097-108.
4. Shipley JL, Butera JN. Acute myelogenous leukemia. Experimental Hematology 2009;37(6):649-58.
5. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of Clinical Oncology 2014;32(27):3059-68.
6. Puissant A, Fenouille N, Alexe G, Pikman Y, Bassil CF, Mehta S, et al. SYK is a critical regulator of FLT3 in acute myeloid leukemia. Cancer Cell 2014;25(2):226-42.
7. Benderra Z, Faussat AM, Sayada L, Perrot JY, Tang R, Chaoui D, et al. MRP3, BCRP, and P-glycoprotein activities are prognostic factors in adult acute myeloid leukemia. Clinical Cancer Research 2005;11(21):7764-72.
8. Sudhindra A, Smith CC. FLT3 inhibitors in AML: are we there yet? Curr Hematol Malig Rep 2014;9(2):174-85.
9. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.
10. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. Journal of Clinical Oncology 2003;21(24):4642-9.
11. Cancer Genome Atlas Research N. Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia. New England Journal of Medicine 2013;368(22):2059-74.
12. Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. Nature 2012;481(7382):506-10.
13. Etienne A, Esterni B, Charbonnier A, Mozziconacci MJ, Arnoulet C, Coso D, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. Cancer 2007;109(7):1376-83.
14. 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.
15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

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.

14. APPENDICES

14.1 Modified Charlson Comorbidity Index

Table 14-1 Modified Charlson Comorbidity Index

Point	Comorbid Condition
1	Myocardial infarction
1	Congestive heart failure
1	Cerebrovascular disease
1	Ulcer
1	Hepatic disease (mild)
1	Diabetes (mild or moderate)
1	Pulmonary disease (moderate or severe)
1	Connective tissue disease
2	Diabetes (severe with end-organ damage)
2	Renal disease (moderate or severe)
2	Solid tumor (without metastases)
3	Hepatic disease (moderate or severe)
6	Solid tumor (with metastases)
	Total score

Source: From Etienne et al, 2007 [13].

14.2 Eastern Cooperative Oncology Group (ECOG) 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 [14].

14.3 Cockcroft-Gault Equation

For male subjects:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For female subjects:

$$\text{Creatinine clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 [15].

14.4 New York Heart Association Classification of Functional Capacity

The following table presents the 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].

14.5 Prohibited CYP3A and P-gp Inducers and Inhibitors

Medication, Supplement, or Food Product[a,b]	Required Washout Period Prior to First Dose
Strong CYP3A Reversible Inhibitors and/or P-gp Inhibitors	
amiodarone azithromycin captopril carvedilol cyclosporine diltiazem dronedarone erythromycin felodipine ketoconazole itraconazole nefazodone posaconazole quercetin quinidine ranolazine ticagrelor verapamil **voriconazole**	5 times the inhibitor half-life (if a reasonable half-life estimate is known), or 7 days (if a reasonable half-life estimate is unknown)
Strong CYP3A Mechanism-Based Inhibitors	
clarithromycin[c] conivaptan[c] mibefradil[c,d] telithromycin	7 days, or 5 times the inhibitor half-life, whichever is longer
Grapefruit-containing foods and beverages	5 days
Strong CYP3A Inducers and/or P-gp Inducers	
avasimibe[e] carbamazepine phenobarbital phenytoin primidone rifabutin rifapentine rifampin St. John's wort	7 days, or 5 times the inducer half-life, whichever is longer

a Note the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/ DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm). If a medication, supplement, or food/beverage is suspected or known to be a or P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list, then its use must be approved on a case by case basis by the Medical

Monitor after consultation with the Clinical Pharmacologist and assessment of the relative benefit and risk.

b Note that medications used to treat HIV or hepatitis C infection that are strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study (with the exception of hydroxyurea for the first 28 days of study drug treatment).

c Also inhibitors of P-gp.

d Withdrawn from the US market due to safety reasons.

e Not marketed in the US.

14.6 Amendment 02 Detailed Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 02 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: To replace signatories who were previously assigned to the protocol.

The primary change occurs on the Signature Page:

Amended text now reads:	PPD

Purpose: To update the proposed number of patients in the study.

The primary change occurs in the Protocol Summary:

Amended text now reads:	Phase 1b dose finding phase: ~~12 to 15~~**approximately 40** patients

Sections that also contain this change are:

- Section 4.1
- Section 4.2
- Section 8.1.1

Purpose: To update language specifying inclusivity of the tyrosine kinase domain mutant populations.

The primary change occurs in the Protocol Summary:

Amended text now reads:	Phase 2 expansion phase: up to 66 based on a Simon's 2-Stage design in both FLT-3 wild type (WT) and FLT-3-internal tandem duplication (ITD) mutant populations **(inclusive of the tyrosine kinase domain [TKD] mutant populations)** ... ...in patients with or without FLT-3 ITD**/TKD** mutation

Section 4.1 also contains this change.

Purpose: To clarify TAK-659 dosage can include BID dosing.

The primary change occurs in Protocol Summary:

Amended text now reads:	• Phase 1b dose finding phase: to determine the safety, tolerability, and maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of TAK-659 administered orally on a **once** daily **(QD) or twice daily (BID)** dosing schedule in patients with relapsed or refractory AML

Sections that also contain this change are:

- Schedule of Events
- Section 2.1
- Section 4.1
- Section 6.1
- Section 6.3

Purpose: To remove the PD effects of TAK-659 (due to the removal of the pS6 sample) and the PD assessment from the Protocol Summary, Secondary Endpoints, Schedule of Events, Overview of Study, and Study Design.

Deleted text from Protocol Summary:	~~To evaluate the pharmacodynamic (PD) effects of TAK-659 against FLT-3 and SYK signaling in circulating AML blasts~~
Deleted row in the Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles] :	~~Blood samples for PD[aa]~~ With assessments at Screening, and Cycle 1, Day 1 and Day 3
Deleted footnote in the Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]:	~~aa Blood specimens for PD analysis will be collected at screening and at time points specified in the AML Dose Escalation (Phase 1b) PK, PD, and ECG Assessment Schedule.~~

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles] also contains this change.

Deleted row in the Schedule of Events for AML	~~Blood samples for PD[z]~~ With assessments at Screening, and Cycle 1, Day 1 and Day 3

Expansion Cohort (Phase 2) [28 Day Cycles]:	
Deleted footnote in the Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles]:	~~z Blood specimens will be collected at screening and at time points specified in AML Dose Expansion (Phase 2) PK, PD Schedule the to evaluate the pharmacodynamic effects of TAK-659 in AML blasts.~~
Deleted columns in AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule AML Dose Expansion (Phase 2) PK Schedule also contains this change.	~~PD~~ columns under Cycle 1, Day 1 and Day 15
Deleted text in Section 3.2:	• ~~PD effect measured as modulation of expression of pathway markers such as pS6 in peripheral AML blasts~~
Amended text in Section 4.1 now reads:	~~PD will be assessed in AML dose escalation and expansion cohorts by evaluating peripheral AML blast at the time points specified in the Schedule of Events. In addition,~~ ~~a~~A plasma inhibitory assay will be used to assess the FLT-3 and possibly SYK inhibitory effects of TAK-659 in vitro using plasma samples collected from patients exposed to TAK-659 at different dose/exposure levels as indicated in the Schedule of Events.
Deleted text in Section 7.4.16:	• ~~Serial blood samples for the determination of PD effects of TAK-659 will be collected at screening and during treatment as outlined in the Schedule of Events. Expression levels of pS6 in AML blast cells will be examined.~~

Purpose: To update the dose escalation status of Study C34001 and specify the MTD as 100 mg.

The primary change occurs in the Protocol Summary:

Amended text now reads: The starting dose for the phase 1b portion of this study (Study C34002) will be directed by the current Study C34001, the first-in-human (FIH) dose escalation study of TAK-659 in patients with advanced solid tumors and lymphoma. The starting dose in Study C34002 will not exceed the highest dose determined to be safe in Study C34001 at the time Study C34002 starts. ~~Thus far in Study C34001, up to 120 mg once daily (QD) of TAK-659 has been evaluated in a total of 11 patients with advanced solid tumors and lymphoma, of whom 8 were evaluable for DLT.~~ A dose of 60 mg QD ~~has been~~**was** determined to be tolerable based on a 3+3 dose escalation schema after evaluation of 6 patients. ~~Dose escalation is ongoing in Study C34001.~~ Based on these data, the starting dose will be 60 mg QD for Study C34002**. Since the initiation of Study C34002, dose escalation has been completed in Study C34001 with 100 mg QD determined as the MTD. In the expansion phase of the ongoing FIH study, lymphoma patients are being evaluated at 100 mg and early clinical activity has been observed in this population. In the Non Hodgkin Lymphoma population, the more relevant target for TAK-659 is SYK.** ~~, unless additional data from Study C34001 indicate a higher dose is safe. A higher starting dose, if supported, will be communicated to investigators in writing at the time of protocol initiation.~~

Sections that also contain this change are:

- Section 4.1
- Section 6.3

Purpose: To allow for prior exposure to investigational FLT-3 inhibitors in the phase 2 portion of the study.

The primary change occurs in the Protocol Summary:

Amended text now reads: For the phase 2 portion of the study, patients must be refractory to or relapsed after no more than 2 prior chemotherapy regimens~~ and must not have prior exposure to any investigational FLT-3 inhibitors~~.

Sections that also contain this change are:

- Section 4.1
- Section 5
- Section 5.1

Purpose: To add CPK testing to the Schedule of Events

The primary change occurs in the Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]:

Added row: **CPK testing[o,p] to coincide with hematology/chemistry timepoints**

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles] also contains this change.

Purpose: To add CMV testing to the Schedule of Events.

The primary change occurs in the Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]:

Added row: **CMV testing[aa]**

	To take place at Screening
With corresponding footnote:	**aa Blood specimen will be collected during screening for a local polymerase chain reaction testing of CMV replication. The CMV viral load data will be entered in the eCRF. Further monitoring of CMV, if indicated, will follow the local standard practice.**

The Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles] also contains this change.

Purpose: To update title of Assessment Schedule.

The primary change occurs in the AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule:

Amended title now reads:	**AML Dose Escalation (Phase 1b) PK, PIA, ~~PD,~~ and ECG Assessment Schedule: Cycle 1**

Purpose: To specify time of day for BID dosing.

The primary change occurs in the AML Dose Escalation (Phase 1b) PK, PIA, and ECG Assessment Schedule:

Amended Footnote now reads:	When the timing of a PK, PIA, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples. **For BID dosing, PK, PIA, and ECG assessment schedule refers to the AM dose.**

The Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles] also contains this change.

This change also occurs in Section 6.1:

Amended text now reads:	Patients should be instructed to take their study medication at approximately the same time each day and to not take more than the prescribed dose at any time. On visit days, patients should be instructed to hold their dose until predose assessments are performed. **For BID dosing, morning and evening doses should be approximately 12 hours apart.** In the event that a patient fails to take the TAK-659 dose at their scheduled dosing time (±6 hours of their scheduled dosing) time **for QD dosing; ±3 hours of their scheduled dosing time for BID dosing)**, that dose should be skipped and the patient must not make dose adjustments on that day or subsequent days to account for the missed dose, for example, by taking a double dose of TAK-659 on the following day. Patients should record any skipped doses in their dosing diary (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

Purpose: To remove specification that subsequent anticancer therapy should not be initiated before recovery from all treatment-emergent toxicities associated with TAK-659.

The primary change occurs in the Schedule of Events for Dose Escalation (Phase 1b) [28-Day Cycles]:

Amended footnote	b End of Study visit will occur 28 days (+ 10 days) after the last dose of study drug or before the start of subsequent anticancer therapy (other than hydroxyurea) if that occurs sooner. ~~Subsequent anticancer therapy should not be initiated before recovery from all~~

now reads: ~~treatment-emergent toxicities associated with TAK-659.~~

Schedule of Events for AML Expansion Cohort (Phase 2) [28 Day Cycles] also contains this change.

Purpose: To update TAK-659 50% inhibition concentration.

The primary change occurs in Section 1.1.2:

Amended text now reads: TAK-659 inhibits purified SYK and FLT-3 enzymes with concentrations producing 50% inhibition (IC_{50}) of ~~4.3~~**3.2** and 4.6 nM, respectively.

Purpose: To update information on the nonclinical experience of TAK-659.

The primary change occurs in Section 1.2:

Amended text now reads: CCI [redacted]

Detailed information regarding the nonclinical pharmacology and toxicology of TAK 659 may be found in the Investigator's Brochure (IB).

Purpose: To update information on the clinical experience of TAK-659.

The primary change occurs in Section 1.3:

Amended text now reads: ~~As of 19 September 2014, TAK-659 has been administered to 11 patients at doses of up to 120 mg once daily (QD). The safety and tolerability of TAK-659 are being evaluated.~~

As of 05 September 2017, 181 patients have been dosed with TAK 659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001 (advanced solid tumors and lymphoma), 32 patients in Study C34002 (R/R AML), 19 patients in Study C34003 (advanced solid tumor) and 9 patients in Study C34005 (advanced NHL). Both the C34001 and C34002 studies are evaluating TAK-659 as a single agent while the C34003 and C34005 studies are evaluating TAK-659 in combination with nivolumab (C34003) and 5 additional combination partners (C34005). Different data cutoff dates were used to provide the most current clinical information, given that the ongoing studies are in various stages of execution. The most current safety and efficacy data for Study C34001 are from the 02 June 2017 data cutoff date. The most current safety and efficacy data for Study C34002 are from the 24 May 2017 data cutoff date. In Study C34003, the TAK-659 dose has been evaluated across 3 dose levels of 60mg, 80mg and 100mg and the MTD determination is pending. In Study C34005, TAK-659 is currently being evaluated at 60 mg with plans to

escalate to 100 mg.

1.3.1 Ongoing Studies With TAK-659

As of 05 September 2017, 181 patients have been dosed with TAK 659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001, 32 patients in Study C34002, 19 patients in Study C34003 and 9 patients in Study C34005.

As of 02 June 2017, in Study C34001, the TAK-659 dose was escalated from 60 mg to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [90 patients], and 120 mg [7 patients]). The maximum tolerated dose (MTD) for patients with lymphoma and solid tumors has been determined to be 100 mg once daily (QD). Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 181 patients treated in this study (92 lymphoma including 5 chronic lymphocytic leukemia [CLL] and 19 solid tumors), 96 patients had discontinued from study by the June data cutoff date. The reasons for discontinuation included PD (45 patients), adverse events (AEs) (29 patients), withdrawal by subject (1 patient), symptomatic deterioration (13 patients), protocol violation (1 patient), initiation of hematopoietic stem cell transplant (2 patients), and other (5 patients).

As of 24 May 2017, in Study C34002, 31 patients had enrolled. TAK-659 has been escalated from 60 mg QD to 160 mg QD, and an additional dose level of 80mg BID is also being evaluated. The MTD/RP2D has not yet been determined. Of the 31 patients treated in this study, 28 patients had discontinued from the study as of the May data cutoff date. The reasons for discontinuation included PD (5 patients), AEs (18 patients), symptomatic deterioration (2 patients), withdrawal by subject (1 patient), and other (2 patients).

The reported AEs were generally as expected on the basis of nonclinical toxicology findings of TAK 659 and the patient populations being studied. As of 02 June 2017, the most common treatment-related AEs reported in Study C34001 (≥20% of patients) have been aspartate aminotransferase (AST) increased (49 patients [44%]), amylase increased (39 patients [35%]), lipase increased (31 patients [28%]), alanine aminotransferase (ALT) increased and diarrhea (28 patients each [25%]), blood creatinine phosphokinase (CPK) increased and hypophosphatemia (26 patients each [23%]), and fatigue (22 patients [20%]). The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (23 patients [21%]), hypophosphatemia (18 patients [16%]), lipase increased (15 patients [14%]), neutropenia (14 patients [13%]), CPK increased (13 patients [12%]), anemia and AST increased (7 patients each [6%]),and pneumonia (5 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase

increased, AST and ALT increased, and blood CPK increased. In Study C34001, as of 02 June 2017, there were 35 on-study deaths. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated varicella, and respiratory failure in the presence of *Pneumocystis jiroveci* pneumonia [PJP]; cytomegalovirus [CMV] and aspergillus infection; and right pneumothorax and renal failure).

In Study C34001, as of 02 June 2017, 9 of the 48 response-evaluable DLBCL patients achieved a complete response (CR) and 4 achieved a partial response (PR). Seven of 10 response-evaluable patients with indolent lymphomas responded (1 CR and 6 PRs). Two out of 4 response-evaluable patients with CLL achieved a response (both PR).

In Study C34002, as of 24 May 2017, there were 15 on-study deaths (one drug related, multiple organ dysfunction syndrome). To date, the safety profile in Study C34002 appears to be similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both peripheral blast and bone marrow blast counts. Three patients have achieved objective response per IWG 2003 criteria (1 CR, 2 CRi) [15] as of the cutoff date.

Purpose: To update details for the PK and biomarker assessments.

The primary change occurs in Section 1.4:

Amended text now reads:

Rationale for Pharmacokinetic Assessments

In the AML Dose Escalation cohorts, blood will be collected during Cycle 1 using an intensive sampling schedule so as to permit the detailed characterization of the plasma pharmacokinetics (PK) of TAK-659. Specifically, serial plasma PK assessments will be used to characterize single- and repeat-dose concentration-time profiles of TAK-659, calculate PK parameters, evaluate the dose-exposure relationship, assess dose- and time-dependence of PK parameters, and contribute to the development of a population PK model for TAK-659. The PK sampling time points are derived from considerations of clinic practicality and patient convenience. Sampling will be conducted on Days 1, 2, 15, and 16 of Cycle 1 to allow evaluation of the accumulation of TAK-659 with ~~daily~~ **QD or twice-daily (BID)** dosing.

In the AML Dose Expansion cohorts, blood will be collected during Cycle 1 **(on Days 1 and 15)** ~~using a sparse sampling schedule~~ to support population PK model development ~~and to interpret the pharmacodynamic (PD) results in relation to the concurrent plasma concentrations of TAK-659. Sampling will be conducted on Days 1 and 15 of Cycle 1~~.

CCI

[redacted]

CCI

[redacted]

Purpose: To update the risks of TAK-659 in nonclinical and clinical studies.

The primary change occurs in Section 1.5:

Amended text now reads:

Because TAK-659 has been administered to **a total of only** ~~11~~ **181 patients as of** ~~19 September 2014 in Study C34001, the ongoing, first-in-human (FIH), dose escalation study of TAK-659 in patients with advanced solid tumors and lymphoma, there are no established benefits of this drug, and~~ **05 September 2017,** it is not currently possible to describe with certainty **the** potential adverse effects of the compound.

1.5.1 Potential Risks From Nonclinical Studies

Potential risks from nonclinical studies in dogs and rats include the **following:**

- **Lymphoid/hematopoietic effects that include** ~~included lymph node~~ **lymphoid** depletion, ~~atrophy,~~ and myelosuppression that ~~were~~ **are** associated with thrombocytopenia, neutropenia, and reticulocytopenia. **These findings may be associated with increased susceptibility to infection, bleeding, and anemia.**
- Epithelial effects on the intestinal tract, urinary tract, and lens. Intestinal effects included minimal-to-slight mucosal hemorrhaging. Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis that led to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.
- Reproductive system effects, including **decreased spermatozoa** and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries.
- Possible mutation of DNA.
- Growth plate thickening and disorganization (not relevant to adults).
- **Lymphoid and hematopoietic effects and reproductive system effects are**

considered important potential risks.

~~In addition, mild to moderate elevations in amylase, lipase, and transaminases were observed after TAK-659 administration in both rats and dogs. However, no signs of injury to the liver or pancreas were observed upon microscopic evaluation. Increased serum lipase and transaminases were observed in a few patients treated with TAK-659 in Study C34001. However, the patients did not have any related symptoms. Further investigations are required to determine the clinical significance of these asymptomatic laboratory abnormalities.~~

~~It is also possible that TAK-659 will have toxicities that were not observed in or predicted from the studies completed in animals.~~

1.5.2 Potential Risks From Clinical Studies

Potential risks based on clinical observations include the following:

On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, asymptomatic lipase or amylase elevations are reported commonly (≥10% of patients). Patients in Study C34002 have frequent monitoring of lipase and amylase as outlined in the Schedule of Events.

Cases of pneumonitis have been reported in clinical studies with B-cell receptor pathway kinase inhibitors, including TAK-659, and pneumonitis is considered an important potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

There have been occurrences of opportunistic infections such as PJP in some patients who had fever. These patients had other underlying conditions that made them prone to infections. With the limited experience we have with TAK-659, we have not determined whether TAK-659 is directly associated with the occurrences of these infections.

Further details regarding the benefits and risks associated with TAK-659 may be found in the current version of the TAK-659 IB.

Purpose: To update the number of patients and study centers.

The primary change occurs in Section 4.2:

Amended text now	For the phase 1b portion, approximately ~~12-15~~**40** patients will be enrolled in this study from approximately ~~2 to 4~~**6** study centers in the United States. For the phase 2 portion, up

reads: to 66 patients will be enrolled in this study from approximately 10 to 15 global sites. Enrollment is defined as time of initiation of the first dose of study drug.

Purpose: To update the study duration.

The primary change occurs in Section 4.3:

Amended text now reads: It is anticipated that this study will last for approximately ~~24 to 32~~**66 to 72** months, including ~~9 to 12~~**304 to 36** months in the phase 1b portion and ~~15 to 20~~**32 to 36** months in the phase 2 portion.

Purpose: To update contraception methods.

The primary change occurs in Section 5.1:

Amended text now reads:

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 **1 highly**~~2~~ effective method~~s~~ of contraception **and 1 additional effective (barrier) method**, at the same time, from the time of signing the informed consent through 180 days 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**, spermicides only, and lactational amenorrhea** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 180 days 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**, spermicides only, and lactational amenorrhea** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

Section 6.6 also contains this change.

Purpose: To update laboratory values regarding lipase and amylase, and to exclude patients with moderate renal impairment.

The primary change occurs in Section 5.1:

Amended text now reads:

9. Clinical laboratory values as specified in the following:
   - Total bilirubin must be ≤1.5 × the upper limit of normal (ULN).
   - Serum ALT and AST must be ≤2.5 × the ULN.
   - **Lipase ≤1.5 × ULN and amylase ≤1.5 × ULN with no clinical symptoms suggestive of pancreatitis or cholecystitis.**
   - ~~Serum creatinine must be < 1.5 × ULN or c~~**C**reatinine clearance ≥**6**~~5~~0 mL/min either as estimated by the Cockcroft-Gault equation (See Section 14.3) or based on urine collection (12 or 24 hours).

Purpose: To clarify exclusion criteria of systemic anticancer treatment.

The primary change occurs in Section 5.2:

Amended text now reads:

4. **Systemic anticancer treatment (including investigational agents)** ~~Prior treatment with investigational agents~~ ≤ 21 days or ≤ 5 × their half-lives ~~(whichever is shorter)~~ before the first dose of study treatment. **(For example, if the 5 × the half-life is shorter than 21 days, 5 x half-life should be used as the washout period. However, a**~~A~~ minimum of 10 days should elapse from prior ~~investigational~~ therapy to initiating protocol therapy.

Purpose: To clarify exclusion criteria regarding use or consumption of substances (medication and supplements).

The primary change occurs in Section 5.2:

Amended text now reads:

14. Use or consumption of any of the following ~~medications, supplements, or foods/beverages that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A within the indicated timeframes below. Note that use or consumption of these substances: is not permitted during the study.~~**substances**:

    a) **Medications or supplements that are known to be i**~~Inhibitors~~ of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. **In general, the use of these agents is not permitted during the study except for AE management (see Section 6.7 for details).** See Section 14.5

for a **nonexhaustive** list of ~~prohibited~~ strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the **US Food and Drug Administration (**FDA**)** Draft DDI Guidance.

b) **Medications or supplements that are known to be s**~~S~~trong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drug. **In general, the use of these agents is not permitted during the study except for AE management (see Section 6.7 for details).** See Section 14.5 for a **nonexhaustive** list of ~~prohibited~~ strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the **US** FDA Draft DDI Guidance.

c) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. **Note that grapefruit-containing food and beverages are not permitted during the study.**

Purpose: To update TAK-659 dose adjustments for nonhematologic toxicities.

The primary change occurs in Table 6-2:

Amended text now reads:

Table 6-2 TAK-659 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 1 week with optimal antiemetics and antidiarrheal following standard of care • Transient Grade 3 fatigue (lasting <1 week) • **Asymptomatic lipase elevation (<Grade 4) in the absence of significant amylase elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators** • **Asymptomatic amylase elevation (<Grade 4) in the absence of lipase elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators** • **Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators** • **Grade 3 hypophosphatemia resolved to**	Hold TAK-659 until resolution to ≤Grade 1 or baseline or a level considered acceptable by the investigator (must be ≤Grade 2). • If resolved in ≤7 days, then maintain dose level. • If resolved in >7 days, then reduce dose by 1 dose level. • If recurrence occurs, then reduce dose by 1 dose level. For the exceptions listed, maintain the dose level **(no dose hold required)**. Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 21 days despite temporary disruption of study drug.

Grade ≤1 or baseline within 72 hours with phosphate repletion • **Other a~~A~~**symptomatic Grade 3 laboratory abnormalities that are considered to be not clinically significant, as determined jointly by the investigators and the sponsor	
Grade 4 nonhematologic toxicities with the exception of: • **Asymptomatic Grade 4 lipase elevation in the absence of significant amylase elevation (<Grade 3).** • **Asymptomatic Grade 4 amylase elevation in the absence of significant lipase elevation (<Grade 3).** • **Asymptomatic Grade 4 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3).** • **Grade 4 hypophosphatemia resolved to ≤Grade 1 or baseline value within 72 hours with phosphate repletion.** • **Other Grade 4 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigator.**	Consider permanently discontinuing TAK-659, except in the case where the investigator determines the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. **Dose reduction of ≥1 dose level is required if study treatment resumes after resolution to ≤Grade 1 or baseline values.** **For the exceptions, hold TAK-659 until resolution to ≤Grade 1 or baseline values or to a level that is clinically acceptable as determined by Investigator (≤Grade 2) , then:** • **If resolved in ≤7 days, maintain dose level.** • **If resolved in >7 days, reduce dose by 1 dose level.** • **If recurs, reduce dose by 1 dose level.**

Purpose: To provide updates to concomitant medications and procedures.

The primary change occurs in the Section 6.5:

Amended text now reads:

6.5 ~~Excluded~~ Concomitant Medications and Procedures

During the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is taking or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the informed consent form (ICF) through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

The following restrictions apply during the study:

~~The following medications and procedures are prohibited during the study:~~

- Any antineoplastic therapy other than TAK-659 (with the exception of hydroxyurea for the first 28 days of study drug treatment). This includes chronic use of corticosteroids at daily doses greater than the equivalent of 10 mg of prednisone as part of any anticancer treatment regimens. If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).

- ~~Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression). Palliative radiotherapy for pain control in a pre-existing lesion may be considered after discussion with the sponsor's clinical representative.~~

- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) in Cycle 1 during dose escalation. Patients who experience severe and/or febrile neutropenia can be managed with growth factor support if needed in accordance with American Society of Clinical Oncology (ASCO) guidelines.

- **Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A should be avoided in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix 14.5 for a nonexhaustive**

list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA draft guidance for DDI studies.

~~Systemic treatment with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A is not permitted in this study because in vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Section 14.5 for a list of excluded medications, supplements, and food products; Section 14.5 also provides the required washout period for these substances prior to the first dose of study drug. Note that medications used to treat HIV or hepatitis C infection are not listed below or in Section 14.5 because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study (with the exception of hydroxyurea for the first 28 days of study drug treatment). If a medication, supplement, or food/beverage is suspected or known to be a or P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list below and in Section 14.5, then its use must be approved on a case by case basis by the Medical Monitor after consultation with the Clinical Pharmacologist and assessment of the relative benefit and risk.~~

- Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
- Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin
- Antimycobacterials: rifabutin, rifampin, rifapentine
- Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone
- Antidepressant: nefazadone
- Immunosuppressant: cyclosporine
- Calcium channel blockers: diltiazem, felodipine, mibefradil, verampamil
- Antiarrhythmics: amiodarone, dronedarone, quinidine
- Antiplatelet: ticagrelor
- Antilipid: avasimibe
- Other cardiovascular: captopril, carvedilol, ranolazine
- Vasopressin antagonist: conivaptan
- Food/Herbals/Supplements: grapefruit-containing food and beverages, St. John's

wort, quercetin

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and Appendix 14.5 may be used for AE management if there is no appropriate alternative treatment available per the investigator's judgment ~~and the dosing is not concurrent with study drug. This situation requires discussion between the investigator and the medical monitor, and the discussion will be documented in the study file. Patients should be closely monitored for potential toxicities~~. **This situation will be handled on a case by case basis, and requires discussion between the investigator and the medical monitor to assess the relative benefit and risk for a given patient. The discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.**

Note that medications used to treat HIV or hepatitis C infection are not listed above or in Appendix 14.5 because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a or P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list above or in Appendix 14.5, then its use must be discussed on a case-by-case basis with the medical monitor or designee to assess the relative benefit and risk. **The discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.**

Purpose: To provide details on managing pneumonitis, edema, hypophosphatemia, enzyme elevations (including transaminase, amylase and lipase, and CPK elevations, in addition to lactate dehydrogenase elevations).

The primary change occurs in Section 6.7:

Added text:

Pneumonitis

Patients with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis after ruling out infectious causes and alternative etiologies. If pneumonitis is suspected, TAK-659 treatment should be interrupted and the patient treated per standard of care. If pneumonitis is moderate/severe, discontinue TAK-659. Patients should be monitored for respiratory signs and symptoms throughout treatment and be advised to promptly report respiratory symptoms.

...

Edema (Including Periorbital)

Peripheral and periorbital oedema have been observed in patients treated with

TAK-659. Management of the event, if it occurs, should follow the standard local practice and dose modification should proceed following the dose modification guideline in Table 6-2.

...

Hypophosphatemia

Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise refer to dose modification guideline in Table 6-2.

Enzyme Elevations

Transaminase, Amylase and Lipase, and CPK Elevations

Elevations of the enzymes above have been observed. Events are generally asymptomatic and reversible with dose interruption. See dose modification guideline in Table 6-2.

Lactate Dehydrogenase Elevations

Lactate dehydrogenase (LDH) elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic and the clinical significance is unknown. No doses have been interrupted due to increased LDH; however, LDH elevations have been observed to be reversible in patients who had TAK-659 interrupted due to other reasons.

Purpose: To provide updated details on managing infections.

The primary change occurs in Section 6.7:

Amended text now reads:

Prophylaxis Against Infections

The severe and prolonged period of neutropenia seen with therapy is frequently associated with neutropenic fevers and a high risk of infection with bacteria or fungi and viral reactivation. To minimize the risk of infection, it is recommended that patients be placed on "neutropenic precaution", with or without the addition of prophylactic antibiotics, antifungals, or antivirals. In addition, patients should be screened for possible infectious foci (eg, dental status).

The components of "neutropenic precaution" may vary by institution but most commonly include: a high efficiency particulate air-filtered room, a diet free of raw berries or vegetables grown in dirt, no sick visitors, and no smoking. In addition, hand washing by all visitors and caregivers should be strictly enforced.

Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis

---

during therapy, particularly if the patient is more prone to developing neutropenia; however, the use of such agents should be at the discretion of investigators based on the local standard practice. Patients who develop neutropenic fever should be evaluated promptly and treated immediately with parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.

Patients with lymphopenia and neutropenia may be more prone to developing infections, such as respiratory tract infections or pneumonia. Consider a diagnosis of opportunistic infection including PJP in patients presenting with shortness of breath, cough, or fever. Prophylaxis for PJP may be initiated (either at baseline or during treatment) if clinically indicated. For older patients, patients with recent exposure to steroids or immunosuppressive agents, or patients who, in the investigator's opinion, are more susceptible to opportunistic infection at baseline, PJP prophylaxis should be considered at the start of the study treatment. When steroids and/or any immunomodulatory agents need to be used to manage the AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is co-administered. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated. However, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

Myelosuppression can also be associated with reactivation of herpes zoster, CMV, herpes simplex and other viruses. Antiviral therapy such as acyclovir, gancyclovir, valacyclovir, or other antiviral agents may be initiated as clinically indicated. Testing of CMV replication by a local polymerase chain reaction (PCR) assay will be required at baseline, and further monitoring and prophylactic or preemptive therapy to asymptomatic patients, if indicated, should follow the institutional standard practice. The following agents should be considered for prophylaxis or preemptive treatment against CMV: ganciclovir intravenously (IV), valganciclovir (orally), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until CMV is no longer detected by PCR.

~~Antiviral prophylaxis, such as acyclovir, is recommended for herpes simplex virus-seropositive patients. The use of prophylactic antibiotics and antifungals should be at the discretion of investigators based on the local standard practice.~~

~~Patients who develop neutropenic fever should be evaluated promptly and treated immediately with parental antibiotics tailored to the prominent organisms and resistance patterns of the institution.~~

Purpose: To provide updated details on managing rash with or without pruritus.

The primary change occurs in Section 6.7:

Amended text now	Prophylactic measures should also be considered if a patient develops a rash (eg, using a

reads: thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. **Treatment with TAK-659 must be withheld in the event of Grade 3 or 4 rash. Refer to dose modification guideline in Table 6-2.**

Purpose: To update temperature of storage conditions to make consistent with other protocols.

The primary change occurs in Section 6.12:

Now reads: TAK-659 tablets should be stored in the original dispensing bottles **at room temperature of 1°C to 25°C (33.8°F to 77°F)**. Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients, returned to sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies received at the clinical sites will be counted and reconciled before being returned to the sponsor.

Purpose: To update language for concomitant medications and procedures.

The primary change occurs in Section 7.4.9:

Now reads: Concomitant medications and procedures will be recorded in the eCRF from the time of the first dose of study drug through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first. See Section 6.5 for a list of medications and therapies that ~~are prohibited~~**should be avoided** during the study **unless otherwise specified**.

Purpose: To update clinical laboratory evaluations to reflect addition of CMV testing.

The primary change occurs in Section 7.4.13:

Amended text now reads: **Clinical Chemistry, Hematology, ~~and~~ Urinalysis, and Virology**

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedule of Events.

...

When creatinine clearance is estimated, the Cockroft-Gault formula will be employed as follows (see Section 14.3):

$$\textit{Estimated creatinine clearance} = [(140 - Age) * Mass(kg)\ ] / [72 * serum\ creatinine(\dots$$

For female patients, the result of the formula above should be multiplied by 0.85.

Virology

- **CMV**

Purpose: To clarify PD population will be derived from the plasma inhibitory assay.

The primary change occurs in Section 8.1.3:

Amended text now reads:	Pharmacodynamics population: Patients with sufficient dosing in Cycle 1 and sufficient pharmacodynamics data **derived from the Plasma Inhibitory Assay** will be used for pharmacodynamics analyses.

Purpose: To remove the PD assessment from the PK analysis.

The primary change occurs in Section 8.1.7:

Deleted text:	~~Plasma PK data from the AML Dose Escalation cohorts and the AML Dose Expansion cohorts may be used to explore the relationship between PD markers of SYK and FLT-3 inhibition and TAK-659 exposure (as described in Biomarker Analysis) and may be used to explore the relationship between exposure and toxicity and exposure and effectiveness using graphical and/or pharmacostatistical approaches, as permitted by the data.~~

Purpose: To update product complaint telephone number.

The primary change occurs in Section 10.11:

Now reads: CCI [redacted]

Purpose: To add CRp, CRh, and CRc to the definition of a response for purposes of disease assessment.

The primary change occurs in Section 7.4.15:

Amended text now reads:

CR, CRi, CRp, CRh, CRc, and PR are defined using the following criteria:

CR: A CR designation requires that the patient achieve the morphologic leukemia-free state and have an ANC of more than 1000/µL and platelets of ≥100,000/µL. A morphologic leukemia-free state requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods. **The peripheral blood should have no leukemic blasts.** Hemoglobin concentration or hematocrit has no

bearing on remission status, although the patient must be independent of transfusions. There should be no residual evidence of extramedullary leukemia.

~~**Morphologic**~~ **CRi (complete response with incomplete recovery of blood counts)**: After chemotherapy, some patients fulfill all of the criteria for CR except for residual neutropenia (<1000/µL) or thrombocytopenia (<100,000/µL).

CRp (complete response without platelet recovery): CRp satisfies all CR criteria except platelets < 100,000/µL, but platelet transfusions are not necessary.

CRh (complete response with partial hematologic recovery): CRh is defined as no evidence of peripheral blasts and partial recovery of peripheral blast counts including ANC above 500/µL and platelets above 50,000/µL.

CRc: A composite complete remission is defined as the sum of patient achieving a CR, CRh, CRi, or CRp.

PR: This designation requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. Thus, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration. A value of ≤5% blasts may also be considered a PR if Auer rods are present.

Response assessments above generally follow the standard criteria except patients who achieve a CR, CRh, CRi, CRp, or PR are not required to be transfusion independent.

Sections that also contain this change are:

- Section 3.1
- Section 4.1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	05-Jan-2018 19:40 UTC
	Biostatistics Approval	05-Jan-2018 21:04 UTC
	Clinical Approval	05-Jan-2018 23:39 UTC