Title: n 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)

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C34002

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)

PHASE 1b/2

Version: 1.0

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PPD

Based on:

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

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_{tau}	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
CLss/F	apparent clearance at steady state
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CR	complete response
CRh	complete response with partial hematologic recovery
Cri	complete response with incomplete hematologic recovery
CRO	contract research organization
CRp	complete response with incomplete platelet recovery
CYP	cytochrome
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	Concentration producing half-maximal response
ECG	electrocardiogram

Abbreviation	Term
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
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma 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
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Term
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
CCI	[redacted]
CCI	[redacted]
PIA	plasma inhibitory assay
PK	pharmacokinetic(s)
PR	partial response
CCI	[redacted]
PTR	peak-trough ratio
QD	once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcB	Bazette'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_{max}	first time to reach maximum plasma concentration
TTP	time to progression
ULN	upper limit of the normal range
WHO	World Health Organization
WT	wild type

4.0 OBJECTIVES

4.1 Primary Objectives

- 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 daily or twice daily 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)

4.2 Secondary Objectives

- 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 pharmacokinetics (PK) of TAK-659 in patients with relapsed or refractory AML

4.3 Exploratory Objectives

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4.4 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 has been 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 NHL 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 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 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, 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 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 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 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 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/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, 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. CCI

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5.0 ANALYSIS ENDPOINTS

Primary Endpoints:

- Dose finding phase: adverse events (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 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 patient achieving a CR, CRh, CRi, or CRp], and partial response [PR])

Secondary Endpoints:

- 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 plasma concentration (C_{max}), first time to reach maximum plasma concentration (t_{max}), area under the plasma concentration versus time curve over the dosing interval (AUC_{tau}), apparent clearance at steady state (CLss/F), accumulation ratio (Rac), and peak-through ratio (PTR)

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6.0 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 $\leq 15\%$, versus an alternative hypothesis of response rate $\geq 35\%$. 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 $\leq 30\%$, versus an alternative hypothesis of response rate $\geq 50\%$. 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4.

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. Cycle 1 day 1 values are considered pre-dose. Screening values are used for baseline values if a Cycle 1 Day 1 value is unavailable.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

For the categorical variables, the count and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. A month is operationally defined to be 30.4375 days.

For the phase 1 analysis, statistical summaries will be descriptive and graphical in nature.

For the phase 2 expansion cohorts, ORR in the response-evaluable population will be tabulated descriptively with 95% exact binomial confidence intervals (CIs). Time-to-event data will be analyzed using 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, FLT-3 mutant cohorts, and overall phase 2 expansion population.

No formal statistical hypothesis testing will be performed.

7.1.1 Data Presentation

In general, data will be presented as follows:

TAK-659 Dose escalation 60 mg QD N=xx	TAK-659 Dose escalation 100 mg QD N=xx	TAK-659 Dose escalation 120 mg QD N=xx	TAK-659 Dose escalation 140 mg QD N=xx	TAK-659 Dose escalation 160 mg QD N=xx	TAK-659 Dose escalation QD Total N=xx

TAK-659 Dose escalation 60 mg BID N=xx	TAK-659 Dose escalation 80 mg BID N=xx	TAK-659 Dose escalation BID Total N=xx	TAK-659 Dose escalation Total N=xx

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

1. If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.4 Conventions for Missing Adverse Event Dates

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

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug
    and
  - on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.

- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug

    and

  - on or before year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
- If the start date of an event is completely missing then the event is assumed to be treatment emergent.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the event will not be considered treatment emergent.

7.1.5 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

1. If the start date has a month and year but the day is missing, the event will be considered concomitant if the month and year of the start date of the event are:
   - On or after the month and year of the date of the first dose of study drug

     and

   - on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
2. If the start date has a year, but the day and month are missing, the event will be considered concomitant if the year of the start date of the event is:
   - On or after the year of the date of the first dose of study drug

     and

   - on or before the year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
3. If the start date of an event is completely missing then the event is assumed to be concomitant.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the event will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing but the end date is missing completely or partially, a similar algorithm should be used to assess whether the end date is before the last dose of study drug plus 28 days to be included.

7.2 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: All enrolled patients who have received at least 1 dose of TAK-659 will be used for all safety analyses.
- Pharmacokinetic population: All 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: All 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: All patients who receive at least 1 dose of study drug, have baseline bone marrow blast counts (use aspirate if available, otherwise use biopsy), and 1 post-baseline 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 at each dose cohort who either experience a DLT during Cycle 1 or complete at least 75% of planned doses of TAK-659 and have sufficient follow-up data to allow both Sponsor and the investigators to determine whether a DLT occurred.

7.3 Disposition of Subjects

The date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, MedDRA Version, WHO Drug Dictionary Version, and SAS Version will be generated in a summary table.

The number of patients in the safety population, in the pharmacokinetics population, in the DLT evaluable population, and the reason study drug was discontinued will be summarized.

All percentages will be based on the number of patients in the safety population.

7.4 Demographic and Other Baseline Characteristics

Summaries of demographic and baseline characteristics will be presented for subjects in the safety population.

The number and percent of patients will be summarized by geographic region, country and site.

Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight. Age will be calculated from date of birth to date of informed consent.

No inferential statistics will be generated.

Baseline characteristics assessments consist of: disease primary diagnosis, years since initial diagnosis, disease type, disease subtype, evidence of extramedullary disease, leukemia cells in central nervous system, revised WHO classification of AML, modified Charlson comorbidity index, risk status (favorable, intermediate, poor), FLT3 status (FLT3-WT or FLT3 Mutant FLT3 Mutant is defined by FLT3-ITD, FLT3-TKD, FLT3-ITD/TKD), other gene mutations (NPM1, CBP1alpha, IDH1, IDH2, KIT, DNMT3A and other gene), Eastern Cooperative Oncology Group (ECOG) performance status.

A separate table will summarize the numbers and percentages of patients who received prior therapy, prior radiation, prior transplant, number of prior anticancer therapies, median number of prior anticancer therapy, type of prior anticancer therapy and best response to the first and last prior anticancer therapies.

7.5 Medical History and Concurrent Medical Conditions

No summary for medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

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

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

The study drug will be dosed continuously 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.

7.7.2 Extent of Exposure

The exposure to TAK-659 will be characterized by duration of treatment in weeks ((last dose date – start dose date + 1)/7), cumulative dose in mg, relative dose intensity (%), number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, ≥6 treated cycles for patients in the safety population. A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Relative dose intensity (RDI) (%) will be presented for cycles 1, 2, …, 6 and overall. Overall RDI is defined as 100 x (total dose received in mg) / (initial prescribed dose per day x number of

treated days). Where the number of treated days is defined as (reference end date for study drug – reference start date for study drug) + 1.

For Relative Dose Intensity by cycle the same formula is used as overall relative dose intensity, but the number of treated days is derived differently. Cycle RDI is defined as 100 x (total dose received in mg in cycle) / (initial prescribed dose per day x number of treated days in cycle). Where the number of treated days in cycle is defined as (last dose date of a cycle – first dose day of cycle) + 1, however, if a patient discontinues during the cycle then use (date of drug discontinuation – first dose day of cycle) + 1.

Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study.

7.7.3 Action on Drug

Action on study drug (e.g. dose reduced due to AE) will be summarized by each cycle (Cycles 1-6), sum of the remainder cycles, and total, for each dose level in the safety population.

7.8 Efficacy Analysis

Analysis of efficacy measures will be descriptive. Antitumor activity of TAK-659 will be based on the best overall response. Investigators will assess disease response following 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 [1] at each time point, and the best overall response for each patient will be derived programmatically from among the reported responses.

7.8.1 Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint for the dose escalation portion of the study.

The primary endpoint for the AML expansion cohort is 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 patient achieving a CR, CRh, CRi, or CRp], and partial response [PR]).

7.8.2 Secondary Efficacy Endpoint(s)

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, TTP, mortality rate at 3 and 6 months, and OS (by FLT-3 mutant cohort, FLT-3 WT cohort, and phase 2 overall).

DOR is defined as the time from the date of first documentation of a response to the date of first documented progressive disease, and DOR will be analyzed for all responders using the Kaplan-Meier method by FLT-3 mutant, FLT-3 WT cohorts and combined phase 2 cohort. For a patient

who has not progressed, duration of response will be censored at the last response assessment that is SD or better.

TTP is defined as the time from the date of first study drug administration to the date of first documentation of PD by the investigator, and TTP will be analyzed based on the response-evaluable population using the Kaplan-Meier method, by FLT-3 mutant, FLT-3 WT populations and phase 2 overall. For a patient that has not progressed, TTP will be censored at the last response assessment that is SD or better.

Comparisons of TTP between the FLT-3 WT and FLT-3-ITD mutant cohorts using log rank test may be carried out when appropriate.

OS is defined as the time from the date of study entry to the date of death, and OS will be analyzed based on the safety population using the Kaplan-Meier method, by FLT-3 mutant, FLT-3 WT populations and overall. For a patient that did not die during the study or lost to follow-up, OS will be censored at the last known surviving date. Comparisons of OS between the FLT-3 WT and FLT-3-ITD mutant cohorts using log rank test will be carried out when appropriate.

In general, 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. The corresponding Kaplan-Meier curves will also be plotted.

ORR is defined as the proportion of patients who achieved CRs, CRps, CRis, CRhs, CRcs and PRs in the response-evaluable population, and ORR will be tabulated. Point estimates as well as 95% binomial confidence intervals will be presented. The number and percentage of patients falling into each response category (eg, CR, CRp, CRi, PR, SD, PD) will be tabulated.

Mortality rate at 3 and 6 months will be summarized and tabulated.

Response rate will also be tabulated by baseline prognostic factors, if applicable. The prognostic factors will include, but will not be limited to, age, any precursor disease (MDS / MPD or not), additional genetic mutation data if available and cytogenetic abnormalities.

7.8.3 Additional Efficacy Endpoint(s)

Additionally, the following will be summarized:

- Percent of patients with at least 50% decrease in bone marrow blast count
- Percent of patients with at least 50% decrease in peripheral blast count.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The PK population will be used for the description of the plasma TAK-659 PK profiles and for the estimation of plasma TAK-659 PK parameters in the AML Dose Escalation cohorts. The specifics of pharmacokinetic analysis are described in a separate Clinical Pharmacology Analysis Plan.

Blood samples for PK analysis will be collected in dose escalation cohorts during Cycle 1 on Days 1, 2, 15 and 16 and in dose expansion cohorts during Cycle 1 on Days 1 and 15.

Pharmacokinetic Concentrations

For escalation cohorts, plasma TAK-659 concentrations will be summarized by nominal time postdose, grouped by dosing schedule, dose level, and dosing cycle and day. For expansion cohorts, plasma TAK-659 concentrations will be summarized by nominal time postdose and grouped by dosing cycle and day. Summary statistics will be reported at nominal sampling times with at least 2 patients in the PK evaluable population; means will be reported if the number of observations above the lower limit of quantitation (NALQ) is ≥ 50% of the number of patients. The summary statistics will consist of: N, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum, and maximum. Plasma concentrations that are BLQ will be set to zero for calculation of summary statistics, except for geometric means, where BLQ values will be considered missing.

Mean and individual plasma TAK-659 concentration data from dose escalation patients will be plotted over time, grouped by dosing schedule, dose level, with separate panels for dosing cycle and day (Cycle 1 Day 1 and Cycle 1 Day 15 only) on both linear and semi-logarithmic scales. Mean concentrations will be plotted by nominal sampling times. Individual concentrations will be plotted by actual sampling times. BLQ values will be plotted as zero on a linear scale and treated as missing on a semi-logarithmic scale.

Mean and individual plasma TAK-659 concentration data from dose escalation patients will be plotted over time, grouped by dosing cycle and day (Cycle 1 Day 1 and Cycle 1 Day 15 only) and with dosing schedule, dose level in separate panels on both linear and semi-logarithmic scales.

Pharmacokinetic Parameters

PK parameters will be estimated for the AML Dose Escalation cohorts (Cycle 1 Day 1 and Cycle 1 Day 15) using non-compartmental methods with WinNonlin® Professional Version 7.0 or higher (Certara USA, Inc., Princeton, NJ). The plasma PK parameters will be estimated from the concentration-time profiles for all PK population patients. In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be considered missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be

used in all computations involving sampling times. If an actual time is missing the nominal time may be used.

All individual patient PK parameter data will be in a data listing. Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum value, and maximum value) will be used to summarize the calculated PK parameters. For t_{max}, only median, minimum value, and maximum value will be presented.

Summary statistics of PK parameter data will be reported for doses with at least 2 patients in the PK parameter population. Individual PK parameters will be listed by patient, dosing schedule, dose group, and dosing cycle and day.

Boxplots will be generated for selected PK parameters i.e. Cycle 1, Day 1 C_{max} versus dose, Cycle 1, Day 15 C_{max} versus dose, Cycle 1, Day 1 AUC_{tau} versus dose, and Cycle 1, Day 15 AUC_{tau} versus dose.

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.

7.10 Pharmacodynamic Analysis

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7.11 Other Outcomes

7.11.1 Pharmacogenomic Analysis

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PPD

7.11.2 Safety Analysis

These analyses will be performed using the safety population. And summaries will be provided by dose level in dose escalation and phase 2 part.

7.11.3 Adverse Events

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. Treatment-emergent AEs are defined as any AE that occurs after administration of the first dose of study treatment and up through 28 days after the last dose of study medication, or until the start of subsequent antineoplastic therapy, whichever occurs first. Treatment-emergent AEs will be tabulated according to the MedDRA by system organ class and preferred terms 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 (i.e., those events reported by ≥10% of all patients in the safety population) by preferred term.
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥10% of all patients in the safety population) by cycle.
- Non-serious treatment-emergent AEs reported by >5% of patients in any dose level in dose escalation part or phase 2 cohort (5% cutoff will be applied before any rounding)
- SAE
- AE leading to discontinuation of the study drug

Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, and once within each preferred term.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation, and on-study deaths.

All grade 3 or higher AEs will be summarized by creatinine clearance <30, 30-60, 60-90, 90-120, >120.

All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 28 days of the last dose of study drug.

7.11.4 Clinical Laboratory Evaluations

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE v4.03. The number and proportion of patients with shifts in NCI CTCAE toxicity grades from baseline to the worst post baseline toxicity grade will be summarized for each dose level in dose escalation part and Phase 2 part for the following tests:

- Hematology: Hemoglobin decreased, Lymphocyte count decreased, Lymphocyte count increased, Neutrophil count decreased, Platelet count decreased, White blood cell count decreased.
- Chemistry: Alanine aminotransferase (ALT) increased, Alkaline phosphatase increased, Aspartate aminotransferase (AST) increased, Bilirubin (total) increased, Creatinine increased, Gamma glutamyl transferase (GGT) increased, Calcium - decreased, Calcium – increased, Glucose – decreased, Glucose – increased, Potassium – decreased, Potassium – increased, Magnesium – decreased, Magnesium – increased, Sodium – decreased, Sodium – increased, Albumin – decreased, Phosphate – decreased, Amylase – increased, Lipase - increased.

Mean laboratory values over time will be plotted for key lab parameters, including Hgb, WBC, lymphocytes, ANC, platelets, phosphate and liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, LDH, creatinine, lipase and amylase for each regimen (overlay line for each dose level and total within each regimen) for all patients up to 6 cycles. A matching summary table will be created.

Baseline and post baseline values of creatinine clearance and LDH will be tabulated. Total LDH will be presented graphically in a spaghetti plot. Temperature over time during Cycle 1 will be presented in boxplot.

7.11.5 Vital Signs

Vital sign results (diastolic and systolic blood pressure, pulse, temperature, and body weight) will be summarized by dose level in dose escalation and phase 2 part as follows:

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

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

7.11.6 12-Lead ECGs

ECG intervals (QT and Bazette's and Fridericia's corrected QT intervals [QTcB and QTcF], PR, QRS, and heart rate) will be summarized by dose levels in dose escalation part and phase 2 part as follows:

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

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value. ECG abnormalities by time point will be tabulated.

In addition, the number and percent of patients with increases >30 ms and >60 ms from pre-dose in QTcF will also be summarized.

7.11.7 Other Observations Related to Safety

Ophthalmology

Any ophthalmic findings that are determined to be abnormal, clinically significant by the investigators will be listed.

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

CR with partial hematologic recovery [CRh] and a composite complete remission [CRc defined as the sum of patient achieving a CR, although mentioned in the protocol amendment 2, the database has not been updated yet to collect these and there were no patients who were enrolled or consented under protocol amendment 2.

Change in definition for response-evaluable population.

8.0 REFERENCES

1. 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.
2. 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.

9.0 DATA LISTINGS

The below subject-level listings will be generated:

- Disposition (date of first dose, date of last dose, number of cycles, reason for discontinuation of study treatment)
- Populations (can be included with disposition listing)
- Demographics
- Baseline characteristics
- Prior therapy
- Concomitant procedures
- Study drug exposure
- TEAEs of grade 3 or higher (cycle date information for the AE onset and end dates will be included)
- TEAEs leading to study drug discontinuation
- TEAEs resulting in dose modifications
- Serious AEs (all SAEs regardless of treatment emergent AE status)
- On-study deaths (defined as death that occurs between the first dose of study drug and 28 days after the last dose of study drug (adverse events with an outcome of death) as well as during follow-up)
- DLTs during Cycle 1
- Pharmacokinetic concentrations
- Pharmacokinetic parameters
- Ophthalmic findings
- Investigator response assessment (including FLT3 mutation status)
- Best response (including FLT3 mutation status)
- Cytogenetic results, risk classification, mutation status (FLT3 and other), prior therapy, duration of response for patients with CR, Cri and PR
- Peripheral blood levels
- Bone marrow levels
- Significant protocol deviations
- Chromosomal abnormalities and genetic mutations
- FLT3 inhibition

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	09-Nov-2018 17:02 UTC
	Clinical Pharmacology Approval	09-Nov-2018 18:37 UTC
	Clinical Approval	09-Nov-2018 21:55 UTC
	Clinical Approval	11-Nov-2018 03:15 UTC
	Biostatistics Approval	12-Nov-2018 15:36 UTC