Cover Page for Protocol

Sponsor name:	FORMA Therapeutics, Inc
NCT number	NCT02719574
Sponsor trial ID:	2102-HEM-101
Official title of study:	A Phase 1/2, Multicenter, Open-label Study of FT-2102 as a Single Agent and in Combination with Azacitidine or Cytarabine in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome with an IDH1 Mutation
Document date:	20 August 2020

*Document date refers to the date on which the document was most recently updated.

CLINICAL STUDY PROTOCOL

STUDY TITLE: A Phase 1/2, Multicenter, Open-label Study of FT-2102 as a Single Agent and in Combination with Azacitidine or Cytarabine in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome with an IDH1 Mutation

Redacted protocol
Includes redaction of personal identifiable information only.

STUDY NUMBER: 2102-HEM-101

STUDY SPONSOR: Forma Therapeutics, Inc.
500 Arsenal Street, Suite 100
Watertown, MA 02472

.

PROTOCOL:	Version 1/ Original	November 30, 2015
	Version 2/ Amendment 1	March 30, 2017
	Version 3/ Amendment 2	October 20, 2017
	Version 4/ Amendment 3	May 16, 2018
	Version 5/ Amendment 4	January 25, 2019
	Version 6/ Amendment 5	January 27, 2020
FINAL:	Version 7/ Amendment 6	August 20, 2020

US IND NUMBER: 127313

EUDRACT NUMBER: 2017-001051-32

[redacted]

SIGNATURE OF CLINICAL INVESTIGATOR

Study Title:	A Phase 1/2, Multicenter, Open-label Study of FT-2102 as a Single Agent and in Combination with Azacitidine or Cytarabine in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome with an IDH1 Mutation
Protocol Number:	2102-HEM-101
Study Sponsor:	Forma Therapeutics, Inc. 500 Arsenal Street, Suite 100 Watertown, MA 02472 Telephone: 617-679-1970 Facsimile: 617-679-1976
Protocol Version:	Version 7/ Amendment 6 August 20, 2020

Declaration of the Investigator:

I confirm that I have read the above protocol, I understand it, and I will work according to the principles of Good Clinical Practices (GCPs) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 56, and 312, and the International Council on Harmonisation (ICH) document "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)" dated March 2018. Further, I will conduct the study in keeping with local legal and regulatory requirements.

_____

Investigator's Signature **Date**

_____

Investigator's Name / Title (Please print)

_____

Institution or Affiliation

SPONSOR SIGNATURE PAGE

Study Sponsor:

Forma Therapeutics, Inc.
500 Arsenal Street, Suite 100
Watertown, MA 61201
Telephone: 617-679-1970
Facsimile: 617-679-1976

Study Director:

[redacted]
Phone:
Fax: [redacted]
Email:
[redacted]

Protocol No. 2102-HEM-101

A Phase 1/2, Multicenter, Open-label Study of FT-2102 as a Single Agent and in Combination with Azacitidine or Cytarabine in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome with an IDH1 Mutation

Protocol History:

Original protocol:	November 30, 2015
Amendment 1	March 30, 2017
Amendment 2	October 20, 2017
Amendment 3	May 16, 2018
Amendment 4	January 25, 2019
Amendment 5	January 27, 2020
Amendment 6	August 20, 2020

[redacted] /20/2020

Forma Therapeutics, Inc.

This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the *Declaration of Helsinki, Title 21* of the *Code of Federal Regulations § 50, 56, and 312*, and *International Council on Harmonisation E6(R2)*.

SERIOUS ADVERSE EVENT REPORTING

CONTACT FORMA THERAPEUTICS PHARMACOVIGILANCE WITHIN 24 HOURS OF LEARNING OF ANY SERIOUS ADVERSE EVENT. IF THE SERIOUS ADVERSE EVENT IS FATAL OR LIFE THREATENING, FORMA THERAPEUTICS PHARMACOVIGILANCE MUST BE INFORMED IMMEDIATELY.

Contact Forma Therapeutics Pharmacovigilance as described below, and complete a Serious Adverse Event report form:

EMAIL OR FAX SAE REPORT FORM TO:	GLOBAL MEDICAL MONITOR	MEDICAL MONITOR ASIA/PACIFIC
Attn: Forma Therapeutics Pharmacovigilance **Fax: 1-617-321-4111** **Email:** safety@formatherapeutics.com	[redacted] **Cell:** [redacted] **Email:** [redacted]	[redacted] **Office:** [redacted] **Cell:** [redacted] **Email:** [redacted]

For reporting of all Serious Adverse Events, Investigators must fax all completed pages of the SAE report form within 24 hours to the following:

ATTENTION: FORMA THERAPEUTICS PHARMACOVIGILANCE

FAX #: 1-617-321-4111 / Email: safety@formatherapeutics.com

To discuss an SAE with the Medical Monitor, contact [redacted] or [redacted] Donato at the numbers provided above. Follow-up information to SAEs must be provided to Forma Therapeutics Pharmacovigilance within 24 hours of Investigator awareness.

SYNOPSIS

STUDY TITLE	A Phase 1/2, Multicenter, Open-label Study of FT-2102 as a Single Agent and in Combination with Azacitidine or Cytarabine in Patients with Acute Myeloid Leukemia or Myelodysplastic Syndrome with an IDH1 Mutation
SPONSOR	Forma Therapeutics, Inc. 500 Arsenal St., Suite 100 Watertown, MA 02472
STUDY RATIONALE	The recent identification of frequent mutations in the isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) genes in human cancers including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) has provided novel therapeutic targets in these diseases (Mardis et al. 2009; Cairns and Mak 2013). IDH mutation-specific inhibitors have been shown to reduce aberrantly elevated levels of the oncometabolite (R)-2-hydroxyglutarate (2-HG), resulting in antitumor efficacy in preclinical models (Rohle et al. 2013; Saha et al. 2014). Inhibition of mutated IDH1 has recently demonstrated efficacy in AML and initial proof-of-concept in MDS patients (Fan et al. 2015; de Botton et al. 2015; DiNardo et al. 2018). IDH1 and IDH2 mutations in AML and glioma result in abnormal hypermethylation of histones and DNA and suppression of normal cellular differentiation. Treatment with the hypomethylating agent azacitidine causes tumor growth inhibition in a patient-derived IDH1-mutated glioma model by reducing DNA methylation and inducing glial differentiation (Borodovsky et al. 2013). Taken together, these data support the combination of FT-2102 and azacitidine in the treatment of patients with AML harboring IDH1 mutations. Low-dose cytarabine (LDAC) is considered a standard of care (SOC) treatment option for AML patients ≥ 60 years who are not candidates for intensive therapy. In a xenograft model, the combination of an IDH1 inhibitor with short duration low dose cytarabine decreased the bone marrow tumor burden better than either treatment alone (Yen et al. 2013). The combination of FT-2102 with LDAC in patients harboring an IDH1 mutation might result in additive clinical benefit.
PRIMARY OBJECTIVES	**Phase 1:** • To determine the maximum tolerated doses (MTDs) or the maximum evaluated doses (MEDs), dose-limiting toxicities (DLTs), and the Phase 2 dose(s) of FT-2102 as a single agent, in combination with azacitidine, and in combination with cytarabine in patients with AML or MDS, harboring the IDH1-R132 mutation **Phase 2:** • To evaluate the antileukemic and antimyelodysplastic activity of FT-2102 as a single agent or in combination with azacitidine in patients with AML or MDS, harboring an IDH1-R132 mutation
SECONDARY OBJECTIVES	**Phase 1:** • To determine the pharmacokinetics (PK) of FT-2102 as a single agent and in combination with azacitidine or cytarabine • To observe patients for any evidence of antileukemic or antimyelodysplastic activity of FT-2102 as a single agent and in combination with azacitidine or cytarabine

	Phase 2: • To confirm the safety of FT-2102 as a single agent and in combination with azacitidine • To evaluate additional measures of the antileukemic or antimyelodysplastic activity of FT-2102 as a single agent and in combination with azacitidine • To determine the PK of FT-2102 as a single agent and in combination with azacitidine
EXPLORATORY OBJECTIVES	**Phase 1 and Phase 2:** • To assess on-target activity of FT-2102, as determined by changes in a pharmacodynamic (PD) biomarker in plasma • To determine the frequency of cancer-associated mutations and/or genetic alterations in responding and nonresponding patients • To evaluate PK/PD and clinical response relationships in each cohort **Phase 2:** • To evaluate the health-related quality of life (QOL) of patients receiving FT-2102 as a single agent or in combination with azacitidine
STUDY ENDPOINTS	**Primary Endpoints** **Phase 1:** • Incidence and severity of adverse events (AEs), clinical laboratory abnormalities and changes in electrocardiogram (ECG) parameters **Phase 2:** • All cohorts except Cohort 2: Complete Response rate (best overall response [BOR] of complete remission [CR]/ complete remission with partial hematological recovery [CRh]) as determined by the investigator per disease-specific criteria. Refer to Appendix 7 for AML and Appendix 8 for MDS response criteria • Cohort 2: Four-month relapse free survival (RFS) rate **Secondary Endpoints** **Phase 1:** • PK parameters derived from FT-2102 concentrations • Antileukemic or antimyelodysplastic activity as determined by CR, CRh, CRi, MLFS, Marrow CR, PR, and SD **Phase 2:** • Evidence of clinical benefit (complete remission with incomplete blood count recovery [CRi], morphologic leukemia-free state [MLFS], Marrow CR, Overall Response [OR], Time to Response [TTR], Duration of Response [DOR], event free survival [EFS], RFS, overall survival [OS], and other definitions of response, including Stable Disease [SD]) • Incidence and severity of adverse events (AEs), clinical laboratory abnormalities and changes in ECG parameters • PK parameters derived from plasma FT-2102 concentrations **Exploratory Endpoints** **Phase 1 and Phase 2:** • Changes in 2-HG levels (PD biomarker) in plasma

	• Cancer-associated mutations and/or genetic alterations • PK/PD in relationship with clinical safety and clinical activity **Phase 2:** Health-related QOL of patients as assessed by a patient-reported questionnaire
STUDY DESIGN	This is a multicenter, open-label Phase 1/2 study of FT-2102 administered orally to patients with AML or MDS. Patients will be given FT-2102 daily in continuous 28-day cycles, alone or in combination with azacitidine or low dose cytarabine until treatment discontinuation. This study is comprised of 3 stages: a Phase 1 dose-escalation stage, a Phase 1 Dose-expansion stage, and a Phase 2 stage. **Phase 1 Dose-escalation Stage:** Dose escalation will be initiated using FT-2102 as a single agent in patients with AML or MDS harboring an IDH1-R132 mutation, as determined by local mutation testing. It is planned that doses of 150 and 300 mg FT-2102 once daily (QD) will be tested. Twice daily (BID) dosing and/or dosing with food to improve on bioavailability may be explored when indicated. On the initial schedule (Schedule 1), FT-2102 will be given orally QD in continuous 28-day cycles. An alternative schedule (Schedule 2) of FT-2102 administered orally BID may be initiated based upon observed PK and clinical observations. This study will utilize a 3+3 dose escalation design, whereby three patients will be treated and if a DLT occurs, then the cohort will be expanded to six patients to determine a non-tolerated dose and MTD. The dose-escalation portion of the study will allow dose increases of up to 50% between cohorts above the 300 mg total daily dose level until the MTD or an MED is determined. Initiation of Schedule 2 will occur following analysis of PK/PD parameters and clinical observations, and may be independent of an MTD in Schedule 1. Dose escalation will stop if an intolerable dose is identified. During the course of dose escalation, a parallel escalation arm will be initiated for FT-2102 in combination with azacitidine in patients with AML or MDS harboring an IDH1-R132 mutation. Dose escalation in the azacitidine combination will initiate following determination of a pharmacodynamically active dose of FT-2102 (single-agent [SA] schedule). The starting dose of FT-2102 in the combination agent is a dose level at which ≤ Grade 2 toxicities (i.e., no Grade 3 or higher toxicities) were observed when FT-2102 was administered as a single agent. This escalation will also enroll patients on a 3+3 design, whereby three patients will be treated and if one DLT occurs, then the cohort will be expanded to six patients; if more than one DLT occurs, escalation will stop at that dose level (or schedule). **Phase 1 Dose-expansion Stage:** Once the MTD or MED has been identified for the SA or azacitidine combination cohorts, up to 14 additional patients may be enrolled in up to 2 expansion cohorts each of SA FT-2102 or in combination with azacitidine in selected populations of patients with AML/MDS harboring IDH1-R132 mutations. These dose-expansion cohorts will evaluate FT-2102 or the combination at doses of FT-2102 ≤ MTD/MED to 1) further define the safety profile of SA FT-2102 or the azacitidine combination and 2) to provide an initial assessment of antileukemic or antimyelodysplastic activity. From these dose expansion cohorts, a recommended Phase 2 dose (RP2D) of FT-2102 as a single agent or in combination with azacitidine will be selected for subsequent evaluation in Phase 2.

	After dose-expansion is complete for FT-2102 as a single agent and FT-2102 in combination with azacitidine, a cohort of 6 patients with AML harboring IDH1 mutation will be treated with FT-2102 in combination with cytarabine 20 mg BID for 10 days, and then cytarabine will be stopped for 18 days. FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days. The starting dose of FT-2102 will be the 150 mg BID dose. Further dose-escalation of FT-2102 in combination with LDAC will not occur beyond 150 mg BID. If > 1 DLTs are observed at the 150 mg BID dose in combination with cytarabine, a lower dose level may be explored. ***Recommended Phase 2 dose*** FT-2102 150 mg BID is the RP2D confirmed for single-agent and azacitidine combination treatment. **Phase 2:** Phase 2 cohorts may include the following: Cohort 1 (SA FT-2102): approximately 173 evaluable patients with R/R AML. To account for potential discordance between local and central mutation testing, approximately 190 patients may be enrolled into this cohort. Cohort 2 (SA FT-2102): approximately 53 patients with AML in morphologic CR/CRi after prior therapy (+/- hematopoietic stem cell transplantation [HSCT]) with residual IDH1-R132 mutation (≥ 0.01%) detected in the bone marrow. Cohort 3 (SA FT-2102): approximately 20 patients with R/R AML/MDS that have been previously treated with FT-2102. Patients who undergo HSCT on-study then relapse post-HSCT are allowed in this cohort. Cohort 4 (FT-2102 in combination with azacitidine): approximately 20 patients with R/R AML/MDS that are naïve to prior hypomethylating therapy and IDH1 inhibitor therapy. Cohort 5 (FT-2102 in combination with azacitidine): approximately 20 patients with R/R AML/MDS that have inadequately responded to or have progressed on prior hypomethylating therapy. Cohort 6 (FT-2102 in combination with azacitidine): approximately 44 patients with R/R AML/MDS who have been previously treated with SA FT-2102 as their last therapy prior to study enrollment. The actual number of patients in this cohort may be larger, since patients from the FT-2102 SA cohorts of this study are allowed to be enrolled in Cohort 6 after their disease progression. Cohort 7 (SA FT-2102): approximately 54 treatment naïve AML patients for whom standard treatments are contraindicated. Cohort 8 (FT-2102 in combination with azacitidine): approximately 28 treatment naïve AML patients who are candidates for azacitidine first line treatment. Safety will be assessed throughout the study. Safety variables assessed will include AEs, concomitant medications, clinical laboratory tests, vital signs measurements, physical examination findings, and ECG readings (see manual for details of Holter monitoring procedures). Efficacy/determination of clinical benefit will be based on investigator's assessment using disease-specific criteria, i.e., derived from the IWG/modified IWG criteria for AML (2003) and MDS (2006).

	Plasma concentrations of FT-2102 will be determined by validated and sensitive bioanalytical methods. The PD biomarker is the change in 2-HG levels in plasma. Assessment of the presence and frequency of cancer-associated mutations and/or genetic alterations will be performed at a central laboratory. Health-related QOL of patients will be assessed by the EuroQol-5D (EQ-5D-5L). The study Schedule of Events are provided in Appendix 1 and Appendix 2.
DURATION	It is estimated that this study will last approximately 48 months. The total duration of study treatment for each patient is expected to be approximately 26 weeks. Study drug will be taken orally and daily (either QD or BID) in 28-day continuous cycles from Day 1 until treatment discontinuation criteria are met. Study treatment should be discontinued if any of the following events occur: • Unacceptable AE or failure to tolerate study therapy • Delay in dosing of > 28 days, without approval of Sponsor • Treatment failure (i.e., progression or relapse) (see Section 4.3, Table 3 for definition) • Hematopoietic Stem Cell Transplant (HSCT) • Withdrawal of consent (no further study participation) • Patient decision to discontinue study treatment • Discretion of the Investigator • Major protocol violation • Pregnancy • Lost to follow-up • Death • Termination of the study by Sponsor Patients will be followed for safety after treatment discontinuation (last dose of study drug) to monitor for AEs for 28 days, or until resolution or stabilization of AEs, except for patients who withdraw consent. Patients who discontinue for reasons other than disease progression/relapse or withdrawal of consent will continue to be followed for response until progression/relapse occurs. Patients who achieve an adequate response to study treatment and meet other criteria required to undergo HSCT may proceed to HSCT after discontinuation of study treatment and will be followed on study for disease evaluation and any new HSCT conditioning or other new antineoplastic therapies received until disease relapse, death, withdrawal of consent, lost to follow-up, or end of study. Additional detail on follow-up for patients who undergo HSCT is provided in Section 4. Patients participating in Phase 1 may be followed for survival for up to 12 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer). Patients participating in Phase 2 may be followed for survival for up to 36 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).
PLANNED TOTAL SAMPLE SIZE	Phase 1: Approximately 110 patients may be enrolled in the dose-escalation and dose-expansion stages. Phase 2: Approximately 429 patients may be enrolled in the 8 proposed Phase 2 cohorts.

TEST ARTICLE, ADMINISTRATION AND DOSE ESCALATION SCHEME

This study may explore multiple potential schedules for FT-2102. On the initial schedule (Schedule 1), FT- 2102 will be given orally QD in continuous 28-day cycles as shown in the following table.

An alternative schedule (Schedule 2) of FT-2102 administered orally BID may be initiated based on observed PK and clinical observations in Schedule 1 (e.g., half-life of FT-2102); the establishment of a MTD in Schedule 1 is not a prerequisite to initiating Schedule 2. The starting dose in Schedule 2 will be calculated from the projected dose level on Schedule 1.

Single-Agent (FT-2102) Schedule 1[a] (Complete)		
Dose Level	**% Increments from prior dose level**	**Dose (mg)**
1	—	150 mg QD
2	Up to 100%	≤ 300 mg QD
3	Up to 50%	≤ 450 mg QD
4	Up to 50%	TBD

Single-Agent (FT-2102) Schedule 2[b] (Complete)		
Dose Level	**% Increments from prior dose level**	**Dose (mg)**
1	—	TBD BID
2	TBD based on safety experience	TBD
3	TBD based on safety experience	TBD
4	TBD based on safety experience	TBD

Combination Agent (FT-2102 + Azacitidine[c]) Schedule 1[a] (Complete)			
Dose Level	**% Increments from prior dose level**	**Dose (mg)**	
		FT-2102	**Azacitidine**
1	—	QD[d]	75 mg/m^2
2	TBD based on safety experience	TBD	75 mg/m^2
3	TBD based on safety experience	TBD	75 mg/m^2
4	TBD based on safety experience	TBD	75 mg/m^2

Combination Agent (FT-2102 + Azacitidine[c]) Schedule 2[b] (Complete)			
Dose Level	**% Increments from prior dose level**	**Dose (mg)**	
		FT-2102	**Azacitidine**
1	—	BID[d]	75 mg/m^2
2	TBD based on safety experience	TBD	75 mg/m^2
3	TBD based on safety experience	TBD	75 mg/m^2
4	TBD based on safety experience	TBD	75 mg/m^2

Combination Agent (FT-2102 + LDAC[c]) Schedule 2 only[b]			
Dose Level	**% Increments from prior dose level**	**Dose (mg)**	
		FT-2102	**LDAC**
1	—	150 mg BID	20 mg BID

AML = acute myeloid leukemia; BID = twice daily; LDAC = low-dose cytarabine; N/A = not applicable; QD = once daily; SA = single agent; TBD = to be determined.

[a] Schedule 1 is QD dosing of FT-2102 on a 28-day schedule.

[b] Schedule 2 is BID dosing of FT-2102 on a 28-day schedule.
Note: Due to a 24-hour PK collection on Cycle 1 Day 2 (C1D2), the second dose of FT-2102 should **not** be administered on Cycle 1 Day 1 (C1D1).

[c] Combination agent (FT-2102 + azacitidine): azacitidine will be administered via subcutaneous injection or intravenous infusion in combination with FT-2102 for seven days, and then azacitidine will be stopped for 21 days. A 48-hour dose-interruption of the azacitidine for weekends or holidays is allowed. FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days.

	[d] The starting dose of FT-2102 in the combination agent is a dose level at which ≤ Grade 2 toxicities (i.e., no Grade 3 or higher toxicities) were observed when FT-2102 was administered as a single agent. [e] After dose-expansion is complete for FT-2102 as a single agent and FT-2102 in combination with azacitidine, a cohort of 6 patients with AML harboring IDH1 mutation will be treated with FT-2102 in combination with cytarabine 20 mg BID for 10 days, and then cytarabine will be stopped for 18 days. FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days. If the PK analysis indicates that absorption/bioavailability of FT-2102 dosed either QD or BID does not increase with increasing dose levels, dose escalation of FT-2102 in the presence of food will be explored. The starting dose of FT-2102 dose-escalation in the presence of food will be a QD dose intended to approximate the FT-2102 exposures already achieved in the clinic and found to be tolerable. Intra-patient dose escalation/dose adjustment within this initial dosing cohort may be considered if the observed exposures fall below the predicted target range. The DLT dose level is defined as the lowest dose level at which DLT is experienced in two or more patients at the same dose level. The MTD is the highest dose level that does not meet the DLT dose level definition. The MED is defined as the highest dose level evaluated when an MTD is not defined. Dose escalation will utilize a 3+ 3 design to define a MTD/MED in one or more selected schedules. For the 3+3 dose escalation design, three patients will be treated at the current dose level. The first cohort of patients will initiate treatment at dose level 1. If no patient experiences a DLT during the Cycle 1 28-day post-dose DLT monitoring period, subsequent dose escalation will proceed as described in the previous table. Dose escalation in the azacitidine combination will initiate following determination of the pharmacodynamically active dose of FT-2102 (single-agent schedule). The starting dose of FT-2102 in the combination agent is a dose level at which ≤ Grade 2 toxicities (i.e., no Grade 3 or higher toxicities) were observed when FT-2102 was administered as a single agent. This escalation will also enroll patients on a 3+3 design, whereby three patients will be treated and if a DLT occurs, then the cohort will be expanded to up to six patients. After dose-expansion is complete for FT-2102 as a single agent and FT-2102 in combination with azacitidine, a cohort of 6 patients with AML harboring IDH1 mutation will be treated with FT-2102 in combination with cytarabine. The starting dose of FT-2102 will be the 150 mg BID dose. Further dose-escalation of FT-2102 in combination with LDAC will not occur beyond 150 mg BID. If > 1 DLTs are observed at the 150 mg BID dose in combination with cytarabine, a lower dose level may be explored. The dose-escalation portion of the study will allow dose increases of up to 50% between cohorts above the 300 mg total daily dose level until the MTD or a MED is determined. Additional intermediate dose levels may be explored as clinically indicated. After discussion between the Investigators and Sponsor, it may be recommended that additional patients be enrolled in one or more cohorts. Patient entry and dose escalation will be based upon occurrence of DLTs in all patients at each dose level. Adverse events will be reviewed with the Investigators and the medical monitor at specific timepoints during the conduct of the study. A review will be performed in the dose-escalation portion of the protocol prior to the opening of a new dose level and to discontinue dose escalation if the MTD has been reached.

	In the 3+3 portion of the dose-escalation phase, three patients will be enrolled in each cohort. • A patient will not be enrolled at the next higher dose level until all patients at the current dose level have completed the 28-day DLT monitoring period. • If one of the initial three patients has a DLT before the end of Cycle 1, the cohort will be expanded to up to six patients. If five of a total of six patients complete the full Cycle without a DLT, escalation may continue.
INCLUSION CRITERIA	1. Pathologically proven AML (except acute promyelocytic leukemia with the t(15;17) translocation) or intermediate, high risk or very high risk MDS as defined by the World Health Organization (WHO) criteria or Revised International Prognostic Scoring System (IPSS-R) **harboring IDH1-R132 mutations**, and one of the following based on enrollment stage or treatment cohort: a. **Single Agent Phase 1 Cohorts including Dose-Escalation/Dose-Expansion:** AML/MDS either R/R to standard therapy, or for whom standard treatments are contraindicated b. **Combination (FT-2102 + azacitidine) Phase 1 Dose-Escalation/ Dose-Expansion (patients must meet one of the following)**: i. Patients with AML that is either R/R to standard therapy, or for whom standard treatments are contraindicated ii. Patients that have MDS that is either R/R to standard therapy, or are treatment-naïve, who are eligible for azacitidine therapy c. **Combination (FT-2102 + Cytarabine) Phase 1 Dose-Escalation/Dose-Expansion Cohort:** Patients ≥ 60 years with treatment-naïve AML for whom standard treatments are contraindicated d. **Phase 2 Cohort 1 (Single Agent) only:** AML R/R to standard therapy e. **Phase 2 Cohort 2 (Single Agent) only:** AML in morphologic CR/CRi after prior therapy (+/- HSCT) with residual IDH1-R132 mutation (≥ 0.01%) detected in the bone marrow f. **Phase 2 Cohort 3 (Single Agent) only:** R/R AML/MDS that have been previously treated with FT-2102 **AND** for whom standard treatments are contraindicated g. **Phase 2 Cohort 4 (FT-2102 + Azacitidine) only:** Patients < 60 years old with R/R AML/MDS with no prior hypomethylating agent therapy **AND** no prior IDH1 inhibitor therapy h. **Phase 2 Cohort 5 (FT-2102 + Azacitidine) only:** R/R AML/MDS that have inadequately responded to or have progressed on prior treatment with a hypomethylating agent i. **Phase 2 Cohort 6 (FT-2102 + Azacitidine) only:** R/R AML/MDS that have been previously treated with single agent FT-2102 as their last therapy prior to study enrollment j. **Phase 2 Cohort 7 (Single Agent) only:** Treatment naïve AML patients for whom standard treatments are contraindicated k. **Phase 2 Cohort 8 (FT-2102 + Azacitidine) only:** Treatment naïve AML patients who are candidates for azacitidine first line treatment.

	• **Note for Phase 2 Cohort 7 and Phase 2 Cohort 8:** Treatment naïve is defined as no prior treatment for AML. Patients may have received a prior treatment for another hematologic malignancy. 2. Patients must have documented IDH1-R132 gene-mutated disease as evaluated by the site 3. Patients ≥ 18 years old 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 3) 5. Signed informed consent prior to beginning study and undergoing procedures 6. No prior solid organ allograft 7. Acceptable liver function: a. Bilirubin ≤ 2 times upper limit of normal (ULN) (≤ 3 times ULN in patients with Gilbert Syndrome) b. Aspartate transaminase (AST, also referred to as SGOT), alanine transaminase (ALT, also referred to as SGPT) and alkaline phosphatase (ALP) ≤ 3 times ULN 8. Acceptable renal function: a. Serum creatinine ≤ 1.5 times ULN or calculated creatinine clearance ≥ 50 mL/min (Cockcroft and Gault 1976) 9. Recovery from the non-hematologic toxic effects of prior treatment to Grade ≤ 1, or baseline value according to NCI CTCAE classification (excluding infertility, alopecia, or Grade 1 neuropathy) 10. Baseline QTcF ≤ 450 msec (average of the QTcF values of screening triplicate ECGs) Note: This criterion does not apply to patients with a bundle branch block (BBB); for patients with BBB, a cardiology consult is recommended to ensure that QTcF is not prolonged. 11. Negative serum pregnancy test if female of childbearing potential 12. For fertile men and women, agreement to use highly effective contraceptive methods for the duration of study participation and 90 days after the last dose of study medication (Section 5.6.1). 13. Agreement for male patients not to donate sperm and for female patients of childbearing potential not to donate ova during the study and for 90 days after the final dose of study drug (Section 5.6.2). 14. **Phase 2 Cohorts 1 - 8 (SA and combination) only:** Pre-treatment peripheral blood and bone marrow aspirate available for retrospective central confirmation of IDH1-R132 mutation is required Note: Central confirmation of IDH1-R132 mutation is not required for study enrollment.
EXCLUSION CRITERIA	1. **Phase 1 Single Agent Dose-escalation/Dose-expansion Cohorts and Phase 2 Cohorts 1, 4, 5, 7 and 8 only:** Patients who have been treated with an IDH1 targeted therapy are excluded

	2. **Phase 2 Single Agent Cohorts 1-3 and 7 only:** Patients with IDH2 mutation detection at baseline or history of IDH2m inhibitor treatment are excluded 3. History of prior malignancy unless disease-free for ≥ 12 months or considered surgically cured; patients with nonmelanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses) 4. Patients with symptomatic central nervous system (CNS) metastases or other tumor location (such as spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc.) necessitating an urgent therapeutic intervention, palliative care, surgery or radiation therapy 5. Patients with previous allogeneic HSCT if they meet any of the following criteria: < 100 days from time of HSCT; active acute or chronic graft vs. host disease (GvHD); or receiving immunosuppressive therapy as treatment or prophylaxis against GvHD Note: Doses < 20 mg methylprednisolone (or its equivalent) daily are not an exclusion criterion. 6. Treatment with radiation therapy, major surgery (requiring general anesthesia) within one month prior to study drug dosing 7. Treatment with chemotherapy or small molecule anticancer therapeutic within five half-lives of the agent or within 21 days if the half-life is unknown. Patients re-enrolling in Cohort 6 after relapse/progression on Cohort 1 are exempt from this washout requirement (i.e. can continue FT-2102 treatment until re-enrollment) 8. Treatment with an anticancer therapeutic antibody less than four weeks before first dose of study drug 9. Treatment with other experimental therapies or participation in another clinical trial within a period of time that is less than the cycle length or within 21 days prior to starting study drug, whichever is shorter 10. Patients unable to swallow oral medications, or patients with gastrointestinal conditions (e.g., malabsorption, resection, etc.) deemed by the Investigator to jeopardize intestinal absorption 11. Congestive heart failure (New York Heart Association Class III or IV) or unstable angina pectoris; previous history of myocardial infarction within one year prior to study entry, uncontrolled hypertension, or uncontrolled arrhythmias (see Appendix 5) 12. Patients with a family history of QT prolongation 13. Concomitant medication(s) known to cause Torsades de Pointes (TdP) initiated less than the duration required to reach steady-state plasma concentration (approximately five half-lives) before first dose of study drug (see Appendix 6) (medications used as needed [PRN] (e.g. Zofran) are exempt) 14. Concurrent treatment with chronic corticosteroids except if chronic treatment with < 20 mg of methylprednisolone daily or equivalent (pulse steroids for treatment or prophylaxis are allowed [e.g., for transfusion or medication reactions])

	15. Known HIV positivity 16. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy (prophylactic systemic antimicrobials permitted) 17. Uncontrolled disease-related metabolic disorder (e.g., hypercalcemia) 18. Pregnant or nursing women or women of childbearing potential not using highly effective contraception; male patients not using highly effective contraception Note: Women of childbearing potential (see Section 5.6) and men must agree to use highly effective contraception (see Section 5.6.1) prior to study entry and for the duration of study participation and 90 days after. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. 19. Serious nonmalignant disease (e.g., hydronephrosis, liver failure, or other conditions) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor 20. Unwillingness or inability to comply with procedures either required in this protocol or considered standard of care 21. Medical, uncontrolled disease-related metabolic disorder, psychiatric, cognitive, or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol, or complete the study 22. History of severe allergic reaction to azacitidine (if patient enrolling into azacitidine combination cohort) or low-dose cytarabine (if patient enrolling into cytarabine combination cohort) 23. Prisoners or patients who are involuntarily incarcerated or are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a patient, if local regulations permit. Strict conditions apply and Forma's approval is required.
DATA EVALUATION	Standardized electronic CRFs (eCRFs) will be constructed for the study. Weekly-twice a month conference calls with each site will be put in place during Phase 1. Monthly conference calls with each site will be put in place during Phase 2. All sites will be monitored approximately every 4-8 weeks, depending on enrollment.
STATISTICAL METHODOLOGY	**Sample Size Considerations:** Dose-escalation stage sample sizes are determined per traditional 3+3 design. The number of patients in the dose-expansion stage is based on safety considerations. Phase 2 sample sizes are as described below. Cohort 1 is based on a group sequential design with one futility interim analysis at the time of ~33% of patients and one efficacy interim analysis at the time of ~66% of patients completing the first response assessments. A total of 173 evaluable patients will have 90% power on a 1-sided 2.5% significance level.

	Cohort 2 is based on a Simon's 2-stage design for a 4-month RFS rate. Overall, 53 patients, with a futility interim at 11 evaluable patients completing the first response assessment, will have approximately 80% power on a 1-sided 2.5% significance level. Cohorts 3, 4, and 5 are designed by controlling the lower limit of the 85% confidence internal for the estimated rate of response to be at least 10% or more. A total of 20 evaluable patients is anticipated to be enrolled in order to estimate the response rate to this degree. Cohort 6 is based on a Simon's 2-stage design for a response rate. With approximately 44 evaluable patients and a futility interim at 14 evaluable patients completing the first response assessment, the cohort would have 80% power on a 1-sided test with a significance level of 5%. Cohort 7 uses a Simon's 2-stage design to test whether the response rate of patients receiving FT-2102 is greater than 25%. Seventeen (17) patients will be enrolled into stage 1, and 37 into Stage 2, for a total of 54 evaluable patients. Assuming the response rate of FT-2102 treated patients is 45%, this design has 80% power on a 1-sided test using a 2.5% significance level. Cohort 8 uses a Simon's 2-stage design to test whether the response rate of patients receiving FT-2102 is greater than 25%. Seven (7) patients will be enrolled into stage 1, and 21 into Stage 2, for a total of 28 evaluable patients. Assuming the response rate of FT-2102 + azacitidine treated patients is 55%, this design has 80% power on a 1-sided test using a 2.5% significance level. **Analysis Populations:** ***DLT-Evaluable Set*** will include all Phase 1 patients who enrolled in the dose escalation cohorts and who have received at least one dose of FT-2102 and completed at least 75% of doses in the first cycle during the DLT evaluation period or have discontinued / interrupted due to adverse events meeting the DLT evaluation criteria. This set will be used for DLT analyses only, unless otherwise specified. ***Safety Analysis Set*** will include all patients who have received at least one dose of study drug (FT-2102, azacitidine, or cytarabine). All safety analyses will be based on the Safety Set unless otherwise specified. Patients will be analyzed under the first dose level received by the patient. ***Full Analysis Set (FAS)*** will include all patients who were enrolled in the study and received at least one dose of FT-2102. This analysis set will be used for efficacy analyses. Patients will be analyzed under the assigned dose. ***Efficacy Evaluable (EE) Set*** will include all patients in Phase 2 Cohort 1 with confirmed IDH1-R132 (by central lab) who have received the first dose of FT-2102 at least 6 months prior to the analysis cutoff date or who have died, progressed, or discontinued study participation. This analysis set is the primary set for Phase 2, Cohort 1 efficacy evaluation. ***Per Protocol (PP) Analysis Set*** is a subset of patients in the EE set, excluding patients who have protocol violations that could impact the evaluation of the efficacy of FT-2102. Some violations that would result in exclusion from the PP Analysis Set are: not meeting all inclusion/ exclusion criteria for a particular cohort, having received chemotherapy not per protocol, received starting dose of FT-2102 other than 150 mg BID, not having at least one post-baseline response assessment. The full list of protocol violations will be reviewed on a de-identified basis by the medical, data management, and statistical leads prior to locking the database, and membership in the PP Analysis Set will be documented and determined based on that review.

	PK Analysis Set consists of patients for whom it is possible to calculate at least one primary PK parameter (e.g. C_{max}, AUC_{last} and AUC_{inf}) and who do not have any major protocol deviations thought to influence the absorption, distribution, metabolism and excretion of the FT-2102. ***PD Analysis Set*** consists of all patients who have received at least one dose of FT-2102 and have completed at least one PD assessment. The PD Analysis Set will be used for PK/PD-related analyses unless otherwise specified. **Efficacy Analyses**: The analyses of response will be based on disease-specific criteria derived by the investigator from the IWG/ modified IWG criteria for AML (2003) and MDS (2006). The primary efficacy endpoint for all Phase 2 cohorts except for Cohort 2 is the complete response rate (CR + CRh), which will be tabulated by study phase, cohort, and dose based on the best overall response. Phase 2 Cohort 1 will test the complete response rate using a 1-sided exact binomial test for one proportion, with a 2.5% significance level. Other Phase 2 cohorts have different hypothesis tests, further described in Section 9.2.2. Additionally, the ORR will be calculated for each cohort, presented with the corresponding 95% confidence intervals, based on exact binomial methods. Number and percentage of patients within other response categories will also be presented by dose/dosing schedule and visit. The primary efficacy endpoint for Phase 2 Cohort 2 is 4-month RFS, further described in Section 9.2.4.3. Analyses of DOR, TTR, EFS, RFS, and OS will be based on Kaplan-Meier methods for each cohort; the median time will be tabulated along with the 95% confidence intervals. **Safety Analyses:** All safety analyses will be descriptive in nature and based on the Safety Set. Number of DLTs, based on the DLT-Evaluable Set, will be summarized by dose level. Safety data, including adverse events, safety laboratory values, vital signs, physical examination findings, and ECG results, will be based on the Safety Set, summarized by study stage and phase and by dose, and listed in the individual data listings as appropriate. For selected safety parameters, National Cancer Institute Common Terminology Criteria for Adverse Events (MedDRA version 19.1) grades and the corresponding shift from baseline grade may be evaluated, based on the Safety Set, if available data permit. Additional efficacy and safety analyses will be specified in the Statistical Analysis Plan.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

Abbreviation	Definition
α-KG	α-ketoglutarate
AE	adverse event
AESI	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT (SGPT)	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST (SGOT)	aspartate transaminase
AUC	area under the concentration curve
BBB	bundle branch block
BID	twice daily
BMA	bone marrow aspirate
BOR	best overall response
BUN	blood urea nitrogen
Bx	biopsy
CBC	complete blood count
CL/F	total body clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete remission
CRh	complete remission with partial hematological recovery
Cri	complete remission with incomplete blood count recovery
Css	concentration at steady state
CTCAE	common terminology criteria for adverse events
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
eCRF	electronic case report form
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	efficacy evaluable
EFD	embryo-fetal developmental
EFS	event-free survival
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GvHD	graft vs. host disease
2-HG	(R)-2-hydroxyglutarate
HNSTD	highest non-severely toxic dose

HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICSH	International Council for Standardization in Hematology
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
IDH1m	isocitrate dehydrogenase 1-mutant
IND	Investigational New Drug
INR	international normalized ratio
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IV	intravenous
IWG	International Working Group
KM	Kaplan-Meier
LDAC	low-dose cytarabine
LH	luteinizing hormone
LFT	liver function test
MDS	myelodysplastic syndrome
MED	maximum evaluated dose
MedRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
OR	overall response
OS	overall survival
PD	pharmacodynamics
PHI	protected health information
PK	pharmacokinetics
PP	per protocol
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QOL	Quality of Life
QTcF	QT interval corrected using Fridericia's formula
RFS	relapse free survival
R/R	relapsed/refractory
RP2D	recommended Phase 2 dose
SA	single agent
SAE	serious adverse event
SAP	Statistical Analysis Plan

SC	subcutaneous
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TBD	to be determined
TdP	Torsades de Pointes
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
TTR	time to response
ULN	upper limits of normal
US	United States
Vd/F	apparent volume of distribution
WBC	white blood cell count
WHO	World Health Organization

1 BACKGROUND

This study will evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity of the novel anticancer drug FT-2102 (olutasidenib), administered to patients with relapsed or refractory acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). FT-2102 is a potent, selective, orally bioavailable, small-molecule inhibitor of mutated isocitrate dehydrogenase 1 (IDH1) being developed by Forma Therapeutics, Inc. and is intended for the treatment of patients harboring IDH1 mutations, in both hematologic and solid tumors.

The presence of mutations at codon 132 in IDH1 imparts a neomorphic activity to the enzyme, resulting in the production of the "oncometabolite" (R)-2-hydroxyglutarate (2-HG), which has pleotropic roles in tumorigenesis. Studies in genetically engineered mouse models and models derived from cancer patient samples support the hypothesis that mutated IDH1 produces 2-HG, the downstream effects of which cause epigenetic changes that consequently block the proper differentiation of progenitor cells and lead to cancer. These data support the therapeutic rationale that inhibition of mutated IDH1 will lower (R)-2-hydroxyglutarate (2-HG) levels and restore normal cellular differentiation.

The promising preclinical data for FT-2102 support its rapid progression into human AML and MDS trials. Additional studies in patients with hematologic malignancies are planned and studies in patients with solid tumors, including central nervous system (CNS) tumors, that harbor an IDH1 mutation, have been initiated.

1.1 Pharmacology

The metabolic enzyme IDH1 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). In both hematologic and solid tumor malignancies, IDH1 mutations lead to aberrant accumulation of 2-HG. 2-HG has been proposed to act as an "oncometabolite" that has pleotropic effects on tumorigenesis. Excess production of 2-HG has been shown to inhibit α-KG-dependent enzymes involved in epigenetic regulation, collagen synthesis, and cell signaling, thereby leading to a block in normal differentiation of progenitor cells and the subsequent development of cancer (Gross et al. 2010; Cairns and Mak 2013; Losman et al. 2013). Therefore, inhibition of mutated IDH1 in tumor cells and the concomitant decrease in 2-HG production is expected to restore normal cellular differentiation and provide therapeutic benefit in IDH1-mutated cancers. Clinical proof-of-concept for this rationale has recently been achieved for an IDH1 inhibitor in patients with IDH1-mutated AML (Fan et al. 2015; de Botton et al. 2015).

1.2 Toxicokinetics

The toxicokinetics of FT-2102 were determined in rats and monkeys following repeat oral twice daily (BID) dosing for 28 consecutive days and for 3 months. Minimal or no dose accumulation was evident in either species. No gender differences were seen in monkeys; however, in rats, FT-2102 exposure (as measured by maximum plasma concentration [C_{max}] and area under the concentration curve [AUC]) was greater in females than in males in both the 1-month and 3-month study. In both species, exposure increased with increasing dose in a less than proportional manner across the dose range evaluated.

1.3 Enzyme-Mediated Drug-Drug Interaction Potential

FT-2102 metabolism is mediated primarily by Cytochrome P450 (CYP). Based on a clinical drug-drug interaction study (2102-HVS-103) inhibition of CYP3A4 does not impact the PK of FT 2102; however, induction of CYP3A4 significantly reduces FT 2102 systemic exposure.

In vitro, FT-2102 showed non-significant, competitive inhibition of the major drug metabolizing CYP enzymes, CYPs 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4 and weak inhibition of CYP2C8. No time-dependent inhibition of CYP3A4 was seen. CYP inhibition-mediated clinical DDIs are not expected.

Based on *in vitro* results, FT-2102 exhibits CYP3A4 induction potential and may impact the PK of co-administered sensitive CYP3A4 substrates through increased clearance.

1.4 Toxicology

A series of studies have been conducted to develop a toxicology profile for FT-2102. The program was comprised of single- and repeat-dose exploratory toxicology studies and definitive 1-month and 3-month toxicology studies conducted in two mammalian species (rat and monkey) using BID dosing of FT-2102 to support the most frequent envisioned dosing schedule in human clinical trials. In addition, dose-range finding and pivotal embryo-fetal developmental (EFD) toxicology studies have been completed in rats.

In the definitive 1-month toxicity study conducted in rats, the no-observed-adverse-effect level (NOAEL) for FT-2102 was considered to be 450 mg/kg/day (225 mg/kg/dose BID), the highest dose administered. Systemic exposure (C_{max} and $AUC_{0\text{-}12\ hr}$) at the NOAEL on Day 28 was 16,700 ng/mL and 107,000 hr·ng/mL, respectively, in males and 25,000 ng/mL and 185,000 hr·ng/mL, respectively, in females. Target organs identified histopathologically in the rat included the liver (centrilobular hypertrophy) and thyroid gland (follicular-cell hypertrophy). The thyroid effects noted in FT-2102-treated rats are considered secondary to the effects noted on the liver and represent a rat-specific mechanism that may not be relevant to human risk. In the 1-month monkey toxicity study, the highest non-severely toxic dose (HNSTD) of FT-2102 was considered to be 50 mg/kg/day, and the NOAEL was considered to be 30 mg/kg/day (15 mg/kg/dose BID). Combined-sex systemic exposure (C_{max} and area under the concentration curve to the last time point [AUC_{Tlast}]) at the NOAEL on Day 28 was 2,490 ng/mL and 23,600 hr·ng/mL, respectively. Noteworthy histopathological findings in monkeys treated with FT-2102 included multinucleated cells in the sinusoids of the liver and atrophy of the intestinal tract. Following the recovery period, intestinal changes were completely reversible, whereas multinucleated cells in the liver were decreased in severity indicating recovery.

In the pivotal 3-month toxicity study conducted in rat, the NOAEL when dosed BID by oral gavage for 3 months was 100 mg/kg/dose (200 mg/kg/day). Systemic exposure (C_{max} and $AUC_{0\text{-}12}$) at the NOAEL on Day 91 was 16,400 ng/mL and 116,000 ng·h/mL, respectively, for males, and 30,200 ng/mL and 236,000 ng·h/mL, respectively, for females. Findings included minimal, reversible clinical pathology changes and minimal to slight microscopic findings and organ weight changes in the kidney, liver, and thyroid (and higher adrenal weights and lower thymus weights with no microscopic findings). In the pivotal 3-month toxicity study in monkey, the HNSTD for FT-2102 when dosed BID by oral gavage for 3 months was 50 mg/kg/day

(25 mg/kg/dose); and the no-observed-effect-level (NOEL) was 30 mg/kg/day (15 mg/kg/dose). At 30 mg/kg/day, this corresponded to combined sex Day 88 C_{max} and AUC_{0-24} values of 3,210 ng/mL and 48,400 ng·h/mL, respectively. At doses >30 mg/kg/day, clinical pathology findings consistent with hepatobiliary injury and impaired biliary function were observed. Microscopic findings in the liver were consistent with the clinical pathology findings. Pathology findings were either completely or partially recovered at the end of the 1-month recovery period, suggesting signs of reversibility.

In a neutral red uptake phototoxicity assay conducted in BALB/c 3T3 mouse fibroblasts, FT-2102 demonstrated phototoxic potential. FT-2102 was found to be negative in the core battery of three pivotal genotoxicity assays that included in vitro bacterial Ames, in vitro micronucleus assay in human lymphocytes, and in the in vivo rat micronucleus assay.

Dose-range finding and pivotal EFD toxicity studies were conducted in the rat. In the pivotal EFD study, the NOAELs were considered to be 250 mg/kg BID for maternal toxicity and 250 mg/kg BID for fetal toxicity (corresponding to an AUC_{0-24} of 406,000 hr·ng/mL and a $C_{max(0-24)}$ of 25,300 ng/mL). No FT-2102-related effects on reproductive performance or cesarean section parameters were observed. No FT-2102-related fetal external or visceral variations or malformations were observed.

1.5 Clinical Rationale

The recent identification of frequent mutations in the IDH1 and isocitrate dehydrogenase 2 (IDH2) genes in human cancers including AML and MDS has provided novel therapeutic targets in these diseases (Mardis et al. 2009; Cairns and Mak 2013). IDH mutation-specific inhibitors have been shown to reduce aberrantly elevated levels of the oncometabolite 2-HG, resulting in antitumor efficacy in preclinical models (Rohle et al. 2013; Saha et al. 2014). Inhibition of mutated IDH1 has recently demonstrated efficacy in AML and initial proof-of-concept in MDS (Fan et al. 2015; de Botton et al. 2015; DiNardo et al. 2018).

IDH1 and IDH2 mutations in AML and glioma result in abnormal hypermethylation of histones and DNA and suppression of normal cellular differentiation.

Treatment with the hypomethylating agent azacitidine causes tumor growth inhibition in a patient-derived IDH1-mutated glioma model by reducing DNA methylation and inducing glial differentiation (Borodovsky et al. 2013). Taken together, these data support the combination of FT-2102 and azacitidine in the treatment of patients with AML harboring IDH1 mutations. Low dose cytarabine (LDAC) is considered a standard of care (SOC) treatment option for AML patients ≥ 60 years who are not candidates for intensive therapy. In a xenograft model, the combination of an IDH1 inhibitor with short duration low-dose cytarabine decreased the bone marrow tumor burden better than either treatment alone (Yen et al. 2013). The combination of FT-2102 with LDAC in the subset of those patients harboring IDH1 mutation might result in additive clinical benefit.

1.5.1 Recommended Phase 2 Dose Selection and Rationale

Once the maximal tolerated dose (MTD) or maximal evaluated dose (MED) has been identified for the single-agent or combination cohorts, selected populations of patients with AML/MDS harboring IDH1-R132 mutations will be enrolled to confirm a recommended Phase 2 dose (RP2D). Up to 14 additional patients may be enrolled into each dose-expansion cohort to confirm and further characterize the safety and clinical activity of FT-2102 as a single agent or in combination with azacitidine. Up to five dose-expansion cohorts may be enrolled at the potential RP2D; two each for single-agent (SA) FT-2102 and in combination with azacitidine and one cohort for FT-2102 in combination with cytarabine.

From these dose-expansion cohorts, an RP2D of FT-2102 as a single agent or in combination will be selected for subsequent evaluation in Phase 2 studies.

A Sponsor review of available safety data in March 2018 (for single agent), and in June 2018 (for azacitidine combination), including a review of all AEs reported in patients treated with the 150 mg BID dose in the expansion cohorts, indicated that the safety profile was consistent with that of patients treated in dose escalation; no new safety signals were observed in the expansion cohorts. Based on this review and with agreement by participating investigators, FT-2102 150 mg BID was declared the RP2D for further evaluation both as single agent and in combination with azacitidine.

2 STUDY OBJECTIVES

Primary Objectives

Phase 1

- To determine the MTDs, the MEDs, dose-limiting toxicities (DLTs), and the RP2Ds of FT-2102 as a single agent, in combination with azacitidine, and in combination with cytarabine in patients with AML or MDS harboring an IDH1-R132 mutation

Phase 2

- To evaluate the antileukemic and antimyelodysplastic activity of FT-2102 as a single agent or in combination with azacitidine in patients with AML or MDS, respectively harboring an IDH1-R132 mutation

Secondary Objectives

Phase 1

- To determine the pharmacokinetics (PK) of FT-2102 as a single agent and in combination with azacitidine or cytarabine
- To observe patients for any evidence of antileukemic or antimyelodysplastic activity of FT-2102 as a single agent and in combination with azacitidine or cytarabine

Phase 2

- To confirm the safety of FT-2102 as a single agent and in combination with azacitidine in select patient populations
- To evaluate additional measures of the antileukemic or antimyelodysplastic activity of FT-2102 as a single agent and in combination with azacitidine
- To determine the PK of FT-2102 as a single agent and in combination with azacitidine

Exploratory Objectives

Phase 1 and Phase 2

- To assess on-target activity of FT-2102, as determined by changes in a pharmacodynamic (PD) biomarker in plasma
- To determine the frequency of cancer-associated mutations and/or genetic alterations in responding and nonresponding patients
- To evaluate PK/PD and clinical response relationships in each cohort

Phase 2

- To evaluate the health-related quality of life (QOL) of patients receiving FT-2102 as a single agent or in combination with azacitidine

3 STUDY ENDPOINTS

Primary Endpoints

Phase 1

- Incidence and severity of adverse events (AEs), clinical laboratory abnormalities and changes in electrocardiogram (ECG) parameters

Phase 2

- All cohorts except Cohort 2: CR rate (best overall response [BOR] of CR/ CRh) as determined by the investigator per disease-specific criteria. Refer to Appendix 7 for AML and Appendix 8 for MDS response criteria
- Cohort 2: Four-month relapse free survival (RFS) rate.

Secondary Endpoints

Phase 1

- PK parameters derived from FT-2102 concentrations
- Antileukemic or antimyelodysplastic activity as determined by CR, CRh, CRi, MLFS, Marrow CR, PR and SD

Phase 2

- Evidence of clinical benefit (CRi, MLFS, Marrow CR, OR, TI, TTR, DOR, EFS, RFS, OS, and other definitions of response, including SD)
- Incidence and severity of adverse events (AEs), clinical laboratory abnormalities and changes in ECG parameters
- PK parameters derived from plasma FT-2102 concentrations

Exploratory Endpoints

Phase 1 and Phase 2

- Changes in 2-HG levels (PD biomarker) in plasma
- Cancer-associated mutations and/or genetic alterations, in bone marrow aspirates and/or peripheral blood
- PK/PD in relationship with clinical safety and clinical activity

Phase 2

- Health-related QOL of patients as assessed by a patient-reported questionnaire

4 STUDY DESIGN

This Phase 1/2 study will utilize a multicenter, open-label, dose-escalation design to evaluate the safety, efficacy, PK, and PD of FT-2102 administered orally to patients with AML or MDS.

Patients will be given FT-2102 daily (QD or BID) in continuous 28-day cycles, alone or in combination with azacitidine (administered at the dose of 75 mg/m^2 for 7 days IV/SC per every 28-day cycle) or LDAC (administered at the dose of 20 mg BID SC for 10 days every 28-day cycle) until treatment discontinuation. The term "study drug" will refer to either FT-2102, azacitidine or cytarabine.

Patients who discontinue for reasons other than disease progression/relapse or withdrawal of consent will continue to be followed for response until progression/relapse occurs.

Patients who achieve an adequate response to study treatment and meet other criteria required to undergo hematopoietic stem cell transplantation (HSCT) may proceed to HSCT after discontinuation of study treatment and will be followed on study for disease evaluation and any new HSCT conditioning or other new antineoplastic therapies received until disease relapse, death, withdrawal of consent, lost to follow-up, or end of study.

If a patient discontinues study drug to undergo HSCT, but is then deemed ineligible for HSCT, the patient may restart study drug with Medical Monitor approval.

Patients who undergo HSCT and then have persistent/recurrent IDH1-mutant (IDH1m) positive disease may be eligible to restart treatment with FT-2102 by re-enrolling in the appropriate Phase 2 cohort with Medical Monitor approval:

- Re-enrollment into Cohort 3 if morphologic relapse/progression

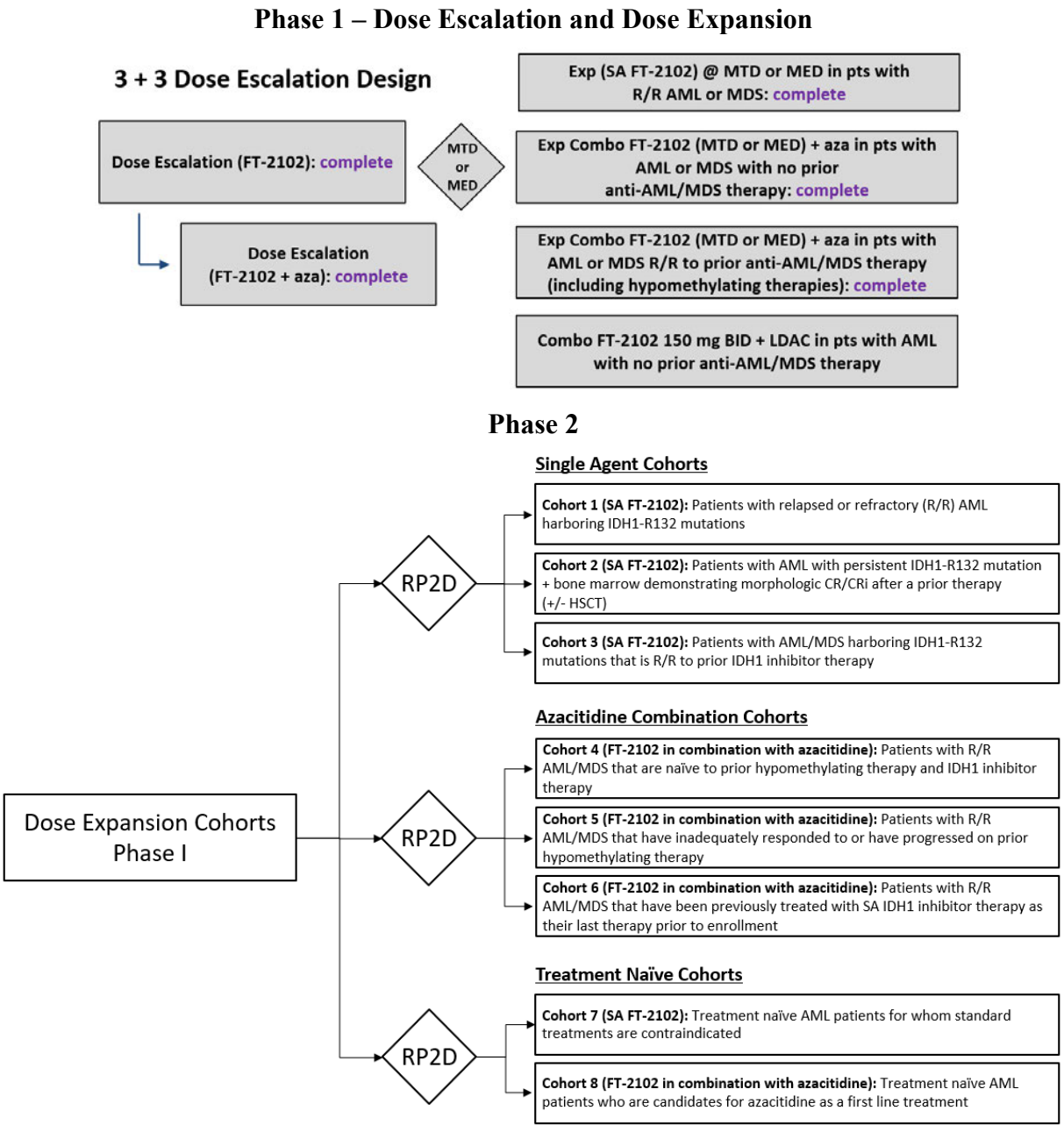
Patients who relapse post-HSCT and elect not to restart FT-2102 treatment will enter the overall survival follow-up period.

Patients participating in Phase 1 may be followed for survival for up to 12 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).

Patients participating in Phase 2 may be followed for survival for up to 36 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).

As shown in Figure 1, the study is comprised of 3 stages: a Phase 1 dose-escalation stage, a Phase 1 dose-expansion stage, and a Phase 2 stage.

Figure 1 Study Design



AML = acute myeloid leukemia; aza = azacitidine; BID = twice daily; combo = combination; Exp = expansion; IDH = isocitrate dehydrogenase; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MED = maximum evaluated dose; MTD = maximum tolerated dose; pts = patients; RP2D = recommended Phase 2 dose; R/R = relapsed/refractory; SA = single-agent.

4.1 Phase 1 Dose-Escalation Stage

4.1.1 Single-Agent (SA) Dose Escalation (Complete)

Dose-escalation will be initiated using SA FT-2102 in patients with AML or MDS harboring an IDH1-R132 mutation, as determined by local mutation testing. FT- 2102 will be given orally QD (Schedule 1) in continuous 28-day cycles at the dose levels proposed in Table 1. It is planned that, at a minimum, doses of 150 mg and 300 mg FT-2102 QD will be tested. Dose increases of up to 50% between cohorts is allowed above the 300 mg total daily dose level until the MTD or MED is determined. Additional intermediate dose levels may be explored as clinically indicated. A BID dose schedule (Schedule 2) may be evaluated as indicated. The starting dose in Schedule 2 will be calculated from the evaluated dose level on Schedule 1. Actual dose level escalations for both schedules will be determined by PK/PD parameters and clinical observations.

Table 1 Single-Agent Dose-Escalation Schema

Single-Agent (FT-2102) Schedule 1 (Complete)		
Dose Level	**% Increments from prior dose level**	**Dose (mg)**
1	—	150 mg QD
2	Up to 100%	≤ 300 mg QD
3	Up to 50%	≤ 450 mg QD
4	Up to 50%	TBD
Single-Agent (FT-2102) Schedule 2 (Complete)		
Dose Level	**% Increments from prior dose level**	**Dose (mg)**
1	—	TBD BID[a]
2	TBD based on safety experience	TBD
3	TBD based on safety experience	TBD
4	TBD based on safety experience	TBD

[a] Due to a 24-hour PK collection on Cycle 1 Day 2 (C1D2), the second dose of FT-2102 should **not** be administered on Cycle 1 Day 1 (C1D1).

In vitro solubility studies of FT-2102 simulating the fed or fasted state indicate that absorption may be increased up to 3-fold if FT-2102 is administered with food. If the observed exposure of FT-2012 QD and/or BID in dose-escalation indicates absorption in the fasted state may be limited, a dose escalation of FT-2102 in the fed state may be evaluated. The starting QD dose of FT-2102 in the fed state will be 3-fold lower than a QD dose evaluated in the fasted state found to be safe and tolerable. Dose escalation in the fed state will continue until the MTD or MED is determined. Intra-patient dose escalation within the first dosing cohort may be allowed in Cycle 1, if the FT-2102 concentration at steady state (Css) is below the intended exposure range.

The dose-escalation stage will utilize a 3+3 design whereby three evaluable patients will be treated at each dose level. The first cohort of patients will initiate treatment at Dose Level 1.

- A patient will not be enrolled at the next higher dose level until all patients at the current dose level have completed the 28-day dose-limiting toxicity (DLT) monitoring period.

- If one of the initial three patients has a DLT before the end of Cycle 1, the cohort will be expanded to up to six patients. If five of a total of six patients complete the full Cycle without a DLT, escalation may continue.
- For a given cohort, once two or more patients have a DLT, further enrollment/treatment for that cohort will halt, as will dose-escalation. The dose level at which two or more of up to six patients have a DLT will be considered to be at least one dose level above the MTD.
- The next lower dose will then be more fully evaluated by treating a total of up to six patients. If two or more patients have a DLT at this lower dose level, de-escalation will continue until a dose level is identified at which zero or one of a total of six patients has a DLT. This will be identified as the MTD.
- Dose-escalation may also stop before an intolerable dose level is identified when continuous PD inhibition is demonstrated.

A DLT is defined below in Section 4.1.3. The DLT dose level is defined as the lowest dose level at which DLT is experienced in two or more patients within a cohort of ≤ 6 patients. The MTD is the highest dose level that does not meet the DLT dose level definition. The MED is the highest dose evaluated in the setting when dose escalation is stopped before an MTD is identified.

Patient entry and dose-escalation will be based upon occurrence of DLTs in all patients at each dose level. Adverse events will be reviewed with the Investigators and the Medical Monitor at specific timepoints during the conduct of the study. A review will be performed in the dose-escalation stage of the protocol prior to the opening of a new dose level and to discontinue dose-escalation if the MTD has been reached.

A minimum of six evaluable patients will be required to confirm the MTD or the MED before proceeding to the dose-expansion phase for SA FT-2102.

Patients will be monitored for safety while on study treatment and for up to 28 days after treatment discontinuation (last dose of study drug) to monitor, or until resolution or stabilization of AEs, except for patients who withdraw consent.

Patients participating in the Phase 1 dose-escalation may be followed for survival for up to 12 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).

4.1.2 FT-2102 + Azacitidine (Combination) Dose-Escalation (Complete)

During the course of SA dose-escalation, a parallel escalation arm will be initiated for FT-2102 in combination with azacitidine in patients with AML or MDS harboring an IDH1-R132 mutation. FT- 2102 will be given orally QD in continuous 28-day cycles as shown in Table 2. The starting dose of FT-2102 in the combination arm will be a dose level at which ≤ Grade 2 toxicities (i.e., no Grade 3 or higher toxicities) were observed when FT-2102 was administered as a single agent. A BID dosing schedule and/or dosing in a fed state may be explored, as indicated.

Table 2 Combination Dose-Escalation Schema

Combination Agent (FT-2102 + Azacitidine) Schedule 1[a] (Complete)			
Dose Level	**% Increments from prior dose level**	**Dose (mg)**	
		FT-2102	**Azacitidine**
1	—	QD	75 mg/m^2
2	TBD based on safety experience	TBD	75 mg/m^2
3	TBD based on safety experience	TBD	75 mg/m^2
4	TBD based on safety experience	TBD	75 mg/m^2
Combination Agent (FT-2102 + Azacitidine) Schedule 2[b] (Complete)			
Dose Level	**% Increments from prior dose level**	**Dose (mg)**	
		FT-2102	**Azacitidine**
1	—	BID	75 mg/m^2
2	TBD based on safety experience	TBD	75 mg/m^2
3	TBD based on safety experience	TBD	75 mg/m^2
4	TBD based on safety experience	TBD	75 mg/m^2

BID = twice daily; QD = once daily; TBD = to be determined.
Note: The starting dose in Schedule 2 will be calculated from the projected dose level on Schedule 1. Actual dose level escalations for both schedules will be determined by PK/PD parameters and clinical observations.
[a] Schedule 1 is QD dosing of FT-2102 on a 28-day schedule.
[b] Schedule 2 is BID dosing of FT-2102 on a 28-day schedule.
Note: With BID schedule, due to a 24-hour PK collection on Cycle 1 Day 2 (C1D2), the second dose of FT-2102 should not be administered on Cycle 1 Day 1 (C1D1).

With the exception of C1D1 and C2D1, when PK sampling is performed, it is recommended that FT-2102 should be administered first on the days when both are given. Azacitidine will be administered per SOC. The recommended dosing schedule for azacitidine is daily × 7 days consecutively (via subcutaneous injection or intravenous infusion), but a 48-hour dose interruption for weekends or holidays is allowed. Azacitidine is to be administered beginning on Cycle 1 Day 1 and then Day 1 of each subsequent 28-day treatment cycle. Alternate schedules for the start of azacitidine administration (e.g., beginning on Day 8 of each treatment cycle) may be evaluated when clinically indicated.

This escalation will also enroll patients on a 3+3 design, whereby three patients will be treated and if one DLT occurs, then the cohort will be expanded to six patients; if more than one DLT occurs, escalation will stop at that dose level (or schedule). Patients who are unable or unwilling to continue treatment with azacitidine after the first treatment cycle may continue participation in the study taking FT-2102 alone, at the discretion of the investigator.

Patient entry and dose-escalation will be based upon occurrence of DLTs in all patients at each dose level. Adverse events will be reviewed with the Investigators and the Medical Monitor at specific timepoints during the conduct of the study. A review will be performed in the dose-escalation stage of the protocol prior to the opening of a new dose level and to discontinue dose-escalation if the MTD has been reached.

A minimum of six evaluable patients will be required to confirm the MTD or the MED before proceeding to the dose-expansion phase for the combination arm.

Patients will continue to be monitored for safety while on study treatment and for up to 28 days after treatment discontinuation (last dose of study drug) or until resolution or stabilization of AEs, except for patients who withdraw consent.

Patients participating in the Phase 1 dose-expansion may be followed for survival for up to 12 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).

4.1.3 Definition of Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as any AE occurring in Cycle 1 that fulfills one or more of the following criteria. Toxicities will be graded and documented according to the NCI CTCAE, version 4.03 guidelines (see Appendix 4):

- Nonhematological Grade 3 or greater toxicity that is unrelated to underlying disease, occurring in Cycle 1 with the following exceptions:
  - Alopecia
  - Grade 3 nausea, vomiting, diarrhea or rash lasting less than 72 hours (with optimal medical management)
  - Grade 3 QTcF prolongation that is < 40 msec increase over baseline in a patient with a bundle branch block (BBB)
  - Grade 3 or 4 toxicity determined to be a sign or symptom of differentiation syndrome that resolves/responds to treatment interventions to < Grade 3 within 7 days (see Section 5.5.1)
- Any Grade 3 non-hematologic laboratory finding, unrelated to underlying disease, occurring in Cycle 1
- Hematologic Grade 4 toxicity as defined by CTCAE on Day 42, in the absence of disease
- Inability to tolerate a minimum of 75% of FT-2102 scheduled doses during Cycle 1 due to an AE. This applies to patients who have their dose held due to AEs per Section 6.8.1.

All patients will be monitored for bone marrow function throughout the study, but these findings may not be considered a DLT unless they fulfill the above criteria.
A DLT is defined within the 28 days of Cycle 1. However, the sponsor will evaluate all safety data, on an ongoing basis, beyond Cycle 1 for determination of an appropriate dose for Phase 2 or later trials.

4.1.4 Phase 1 Dose-Expansion Stage

The following expansion cohorts are proposed:

1. SA FT-2102 at the MTD or MED in patients with relapsed or refractory (R/R) AML or MDS

2. SA FT-2102 at a dose less than the MTD or MED (only if MTD or MED > 150 mg QD) in patients with R/R AML or MDS

3. Combination FT-2102 (MTD or MED) + azacitidine in patients with AML or MDS with no prior anti-AML/MDS therapy

4. Combination FT-2102 (MTD or MED) + azacitidine in patients with AML or MDS that is R/R to prior anti-AML/MDS therapy (including hypomethylating therapies)

Patients will continue to be monitored for safety while on study treatment and for up to 28 days after treatment discontinuation (last dose of study drug) or until resolution or stabilization of AEs, except for patients who withdraw consent. Patients will also be monitored for evidence of antileukemic or antimyelodysplastic activity (Section 4.3).

Patients participating in the dose-expansion cohorts may be followed for survival for up to 12 months from C1D1 or for 28 days after treatment discontinuation (whichever is longer).

FT-2102 in combination with cytarabine:

After dose-expansion is complete for FT-2102 as a single agent and FT-2102 in combination with azacitidine, a cohort of 6 patients with AML harboring IDH1 mutation will be treated with FT-2102 in combination with cytarabine 20 mg BID for 10 days, and then cytarabine will be stopped for 18 days. FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days. The starting dose of FT-2102 will be 150 mg BID. Further dose-escalation of FT-2102 in combination with cytarabine will not occur beyond 150 mg BID.

If ≥ 1 DLTs are observed at the 150 mg BID dose in combination with cytarabine, a lower dose level of FT-2102 may be explored.

4.2 Phase 2 Stage

Specific populations of patients with AML/MDS harboring IDH1-R132 mutations will be enrolled to further characterize the safety and efficacy of FT-2102 at the RP2D in Phase 2 cohorts. Only 1 dose level of FT-2102 as SA and 1 dose level of FT-2102 in combination with azacitidine will be evaluated in the proposed Phase 2 cohorts.

FT-2102 150 mg BID is the RP2D (see Section 1.5.1). This RP2D has been confirmed for SA and azacitidine combination treatment.

Phase 2 cohorts may include the following:

Single-Agent Cohorts:

Cohort 1 (SA FT-2102): approximately 173 evaluable patients with R/R AML. To account for discordance between local and central mutation testing, approximately 190 patients may be enrolled into this cohort to obtain 173 evaluable patients.

Cohort 2 (SA FT-2102): approximately 53 patients with AML in morphologic CR/CRi after prior therapy (+/- HSCT) with residual IDH1-R132 mutation (≥ 0.01%) detected in the bone marrow.

Cohort 3 (SA FT-2102): approximately 20 patients with R/R AML/MDS that have been previously treated with FT-2102. Patients who undergo HSCT on-study then relapse post-HSCT are allowed in this cohort.

Azacitidine Combination Cohorts:

Cohort 4 (FT-2102 in combination with azacitidine): approximately 20 patients with R/R AML/MDS that is naïve to prior hypomethylating therapy and IDH1 inhibitor therapy.

Cohort 5 (FT-2102 in combination with azacitidine): approximately 20 patients with R/R AML/MDS that have inadequately responded to or have progressed on prior hypomethylating therapy.

Cohort 6 (FT-2102 in combination with azacitidine): approximately 44 patients with R/R AML/MDS that have been previously treated with SA FT-2102 as their last therapy prior to study enrollment. The actual number of patients in this cohort may be larger, since patients from the FT-2102 SA cohorts of this study are allowed to be enrolled in Cohort 6 after their disease progression.

Treatment Naïve Cohorts:

Cohort 7 (SA FT-2102): Approximately 54 treatment naïve AML patients for whom standard treatments are contraindicated.

Cohort 8 (FT-2102 in combination with azacitidine): Approximately 28 treatment naïve AML patients who are candidates for azacitidine as a first line treatment.

> **Note for Phase 2 Cohort 7 and Phase 2 Cohort 8:** Treatment naïve is defined as no prior treatment for AML. Patients may have received a prior treatment for another hematologic malignancy.

Patients will be monitored for safety while on study treatment and for up to 28 days after treatment discontinuation (last dose of study drug) or until resolution or stabilization of AEs, except for patients who withdraw consent.

4.3 Response Assessment

All patients participating in this study will undergo response assessments through evaluation of clinical findings and bone marrow/peripheral blood cell counts and morphology. Criteria to guide the investigator's assessment of response are defined in Table 3 below and Appendix 7 and Appendix 8.

Bone marrow for response assessment is required at:

- C2D1 if no peripheral blasts; otherwise, at C3D1, regardless of peripheral blast count
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6

- For patients with AML, every 6 cycles thereafter unless there is a suspicion of relapse/progression
- For patients with MDS, to be performed as clinically indicated
- When progressive disease is suspected
- The same assessment frequency should carry on post-HSCT
- For Phase 2 Cohort 2 only: bone marrow assessment should be done at C2D1, C4D1, C6D1, and only if relapse is suspected thereafter

Response criteria are derived from the International Working Group (IWG) response criteria for AML (2003) and MDS (2006) where applicable; refer also to Stein et al. 2017.

In general, HSCT is not considered an event in time to event analyses. Patients who stop treatment with FT-2102 to have HSCT will continue to be monitored for duration of response. HSCT is not considered an anti-leukemia therapy for purposes of analyses described herein.

Table 3 Response Assessment Criteria

Per Protocol Response Criterion[a,b]	Corresponding IWG Response/ Modified Response Criteria	
	AML (2003)	MDS (2006)
Morphologic Complete Remission	CR[c]	CR
CR with partial hematologic recovery	CRh	Not applicable
CR with incomplete blood count recovery	CRi	Marrow CR
Morphologic leukemia-free state	MLFS	Not applicable
Partial Response	PR	PR
Stable Disease[d]	Stable Disease[d]	Stable Disease
Treatment Failure	Progressive disease (PD) [e] /Relapse	Relapse /PD

AML = acute myelogenous leukemia; CR = complete remission; CRh = complete response with partial hematologic recovery; CRi = complete remission with incomplete blood count recovery; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial response.
Source: Cheson et al. 2003; Cheson et al. 2006 ; Stein et al. 2017

[a] Additional response criteria per IWG (e.g., cytogenetic or molecular complete remission) may be collected when available or provided. However, investigators will be asked to provide response assessment corresponding to the per protocol response criteria outlined.

[b] For MDS, responses must last at least 4 weeks (i.e., confirmation required at 4 weeks) and hematologic improvements (HI) must last at least 8 weeks. For AML, no minimum duration of response required to qualify for a given response.

[c] The assessment frequency for CR should also be applied to patients in CRm and CRc. Please refer to Appendix 7 for definitions.

[d] Stable Disease (SD) is defined as failure to achieve a partial response but not meeting criteria for progressive disease. SD lasting for a period of more than 8 weeks is considered clinical benefit

[e] Progressive disease (PD) in AML is defined as previously having demonstrated partial remission or stable disease. For those with 5% to 66% bone marrow blasts at nadir, a > 50% increase in bone marrow blast count percentage from the nadir and percentage is ≥ 20%; and for patients with ≥ 67% bone marrow blasts at nadir, a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count > 10×10^9/L

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet ALL inclusion criteria listed below:

1. Pathologically proven AML (except acute promyelocytic leukemia with the t(15;17) translocation) or intermediate risk, high risk or very high risk MDS as defined by the World Health Organization (WHO) criteria or Revised International Prognostic Scoring System (IPSS-R) **harboring IDH1-R132 mutations**, and one of the following based on enrollment stage or treatment cohort:

    a. **Single Agent Phase 1 Cohorts including Dose-Escalation/ Dose-Expansion:** AML/MDS either R/R to standard therapy, or for whom standard treatments are contraindicated

    b. **Combination (FT-2102 + azacitidine) Phase 1 Dose-Escalation/ Dose-Expansion (patients must meet one of the following)**:
        i. Patients with AML that is either R/R to standard therapy, or for whom standard treatments are contraindicated
        ii. Patients with MDS that is either R/R to standard therapy, or are treatment-naïve, who are eligible for azacitidine therapy

    c. **Combination (FT-2102 + cytarabine) Phase 1 Dose-Escalation/Dose-Expansion Cohort:** Patients ≥ 60 years with treatment-naïve AML for whom standard treatments are contraindicated

    d. **Phase 2 Cohort 1 (Single Agent) only:** AML R/R to standard therapy

    e. **Phase 2 Cohort 2 (Single Agent) only:** AML in morphologic CR/CRi after prior therapy (+/- HSCT) with residual IDH1-R132 mutation (≥ 0.01%) detected in the bone marrow

    f. **Phase 2 Cohort 3 (Single Agent) only:** R/R AML/MDS that have been previously treated with FT-2102 **AND** for whom standard treatments are contraindicated

    g. **Phase 2 Cohort 4 (FT-2102 + Azacitidine) only:** Patients < 60 years old with R/R AML/MDS with no prior hypomethylating agent therapy **AND** no prior IDH1 inhibitor therapy

    h. **Phase 2 Cohort 5 (FT-2102 + Azacitidine) only:** R/R AML/MDS that have inadequately responded to or have progressed on prior treatment with a hypomethylating agent

i. **Phase 2 Cohort 6 (FT-2102 + Azacitidine) only:** R/R AML/MDS that have been previously treated with single agent FT-2102 as their last therapy prior to study enrollment

j. **Phase 2 Cohort 7 (Single Agent) only:** Treatment naïve AML patients for whom standard treatments are contraindicated

k. **Phase 2 Cohort 8 (FT-2102 + Azacitidine) only:** Treatment naïve AML patients who are candidates for azacitidine as a first line treatment

- **Note for Phase 2 Cohort 7 and Phase 2 Cohort 8:** Treatment naïve is defined as no prior treatment for AML. Patients may have received a prior treatment for another hematologic malignancy.

2. Patients must have documented IDH1-R132 gene-mutated disease as evaluated by the site

3. Patients ≥ 18 years old

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 3)

5. Signed informed consent prior to beginning study and undergoing procedures

6. No prior solid organ allograft

7. Acceptable liver function:
   a. Bilirubin ≤ 2 times upper limit of normal (ULN) (≤ 3 times ULN in patients with Gilbert Syndrome)
   b. Aspartate transaminase (AST, also referred to as SGOT), alanine transaminase (ALT, also referred to as SGPT) and alkaline phosphatase (ALP) ≤ 3 times ULN

8. Acceptable renal function:
   a. Serum creatinine ≤ 1.5 times ULN or calculated creatinine clearance ≥ 50 mL/min (Cockcroft and Gault 1976)

9. Recovery from the non-hematologic toxic effects of prior treatment to Grade ≤ 1, or baseline value according to NCI CTCAE classification (excluding infertility, alopecia, or Grade 1 neuropathy)

10. Baseline QTcF ≤ 450 msec (average of the QTcF values of screening triplicate ECGs)

Note: This criterion does not apply to patients with a bundle branch block (BBB); for patients with BBB, a cardiology consult is recommended to ensure that QTcF is not prolonged.

11. Negative serum pregnancy test if female of childbearing potential

12. For fertile men and women, agreement to use highly effective contraceptive methods for the duration of study participation and 90 days after the last dose of study medication (Section 5.6.1)

13. Agreement for male patients not to donate sperm and for female patients of childbearing potential not to donate ova during the study and for 90 days after the final dose of study drug (see Section 5.6.2)

14. **Phase 2 Cohorts 1 - 8 (SA and combination) only:** Pre-treatment peripheral blood and bone marrow aspirate available for retrospective central confirmation of IDH1-R132 mutation is required.
Note: Central confirmation of IDH1-R132 mutation is not required for study enrollment.

4.4.2 Exclusion Criteria

To be eligible for entry into the study, the patient must NOT meet any of the exclusion criteria listed below:

1. **Phase 1 Single Agent Dose-escalation/Dose-expansion Cohorts and Phase 2 Cohorts 1, 4, 5, 7 and 8 only:** Patients who have been treated with an IDH1 targeted therapy are excluded

2. **Phase 2 Single Agent Cohorts 1-3 and 7 only:** Patients with IDH2 mutation detection at baseline or history of IDH2m inhibitor treatment are excluded

3. History of prior malignancy unless disease-free for ≥ 12 months or considered surgically cured; patients with nonmelanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses)

4. Patients with symptomatic central nervous system (CNS) metastases or other tumor location (such as spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc.) necessitating an urgent therapeutic intervention, palliative care, surgery or radiation therapy

5. Patients with previous allogeneic HSCT, if they meet any of the following criteria: < 100 days from time of HSCT; active acute or chronic graft vs. host disease (GvHD); or receiving immunosuppressive therapy as treatment or prophylaxis against

GvHD
Note: Doses < 20 mg methylprednisolone (or its equivalent) daily are not an exclusion criterion.

6. Treatment with radiation therapy, major surgery (requiring general anesthesia) within one month prior to study drug dosing

7. Treatment with chemotherapy or small molecule anticancer therapeutic within five half-lives of the agent or within 21 days if the half-life is unknown. Patients re-enrolling in Cohort 6 after relapse/progression on Cohort 1 are exempt from this washout requirement (i.e. can continue FT-2102 treatment until re-enrollment)

8. Treatment with an anticancer therapeutic antibody less than four weeks before first dose of study drug

9. Treatment with other experimental therapies or participation in another clinical trial within a period of time that is less than the cycle length or within 21 days prior to starting study drug, whichever is shorter

10. Patients unable to swallow oral medications, or patients with gastrointestinal conditions (e.g., malabsorption, resection, etc.) deemed by the Investigator to jeopardize intestinal absorption

11. Congestive heart failure (New York Heart Association Class III or IV) or unstable angina pectoris; previous history of myocardial infarction within one year prior to study entry, uncontrolled hypertension, or uncontrolled arrhythmias (see Appendix 5)

12. Patients with a family history of QT prolongation

13. Concomitant medication(s) known to cause Torsades de Pointes (TdP) initiated less than the duration required to reach steady-state plasma concentration (approximately five half-lives)before first dose of study drug (see Appendix 6) (medications used as needed [PRN] (e.g. Zofran) are exempt)

14. Concurrent treatment with chronic corticosteroids except if chronic treatment with < 20 mg of methylprednisolone daily or equivalent (pulse steroids for treatment or prophylaxis are allowed [e.g., for transfusion or medication reactions])

15. Known HIV positivity

16. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy (prophylactic systemic antimicrobials permitted)

17. Uncontrolled disease-related metabolic disorder (e.g., hypercalcemia)

18. Pregnant or nursing women or women of childbearing potential not using highly effective contraception; male patients not using highly effective contraception
Note: Women of childbearing potential (see Section 5.6) and men must agree to use highly effective contraception (see Section 5.6.1) prior to study entry and for the duration of study participation and 90 days after.

    Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

19. Serious nonmalignant disease (e.g., hydronephrosis, liver failure, or other conditions) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor

20. Unwillingness or inability to comply with procedures either required in this protocol or considered standard of care

21. Medical, uncontrolled disease-related metabolic disorder, psychiatric, cognitive, or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol, or complete the study

22. History of severe allergic reaction to azacitidine (if patient enrolling into azacitidine combination cohort) or low-dose cytarabine (if patient enrolling into cytarabine combination cohort)

23. Prisoners or patients who are involuntarily incarcerated or are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness
Note: Under certain specific circumstances, a person who has been imprisoned may be included or permitted to continue as a patient, if local regulations permit. Strict conditions apply and Forma's approval is required.

Note: Eligibility criteria waivers will not be granted.

4.5 Study Assessments

The assessments for this study are listed in Section 6.1.

4.6 Replacement of Dropouts in Phase 1 Dose-Escalation Cohorts

Patients participating in Phase 1 dose-escalation cohorts who discontinue early before completing Cycle 1 for any reason other than an AE may not be evaluable and therefore may be replaced at the discretion of the Sponsor. To be considered evaluable, patients must have

completed a minimum of 75% of FT-2102 scheduled doses during Cycle 1, except those experiencing a DLT. All patients who come off study should complete both an end-of-study and a 28-day follow-up evaluation.

5 STUDY DRUG INFORMATION AND DOSAGE

5.1 Identification and Description of Test Articles

5.1.1 FT-2102

FT-2102 capsules incorporate FT-2102 active pharmaceutical ingredient (API) powder blended with compendial grade excipients to impart suitable flow and dissolution properties, and are subsequently filled in a Coni-Snap® hard gelatin capsule. FT-2102 Capsules are initially presented as two unit strengths for oral administration. The capsules contain 50 or 150 mg FT-2102 fill weight per capsule. Each dose strength is filled in white capsules that have a distinctive size.

- Size 2 White/White opaque capsules are filled with formulated bulk that contains 50 mg FT-2102.
- Size 00 White/White opaque capsules are filled with formulated bulk that contains 150 mg FT-2102.

5.1.2 Azacitidine

Azacitidine is supplied as a lyophilized powder in 100 mg single-use vials containing no preservative and is packaged in cartons of one vial.

5.1.3 Cytarabine

Cytarabine Injection is supplied as 20 mg/mL clear, colorless sterile isotonic solution, which contains no preservative, and is packaged in cartons of one vial.

5.2 Administration, Storage and Handling of Test Articles

5.2.1 FT-2102

FT-2102 capsules shall be stored according to storage conditions provided on the drug product label.

FT-2102 will be administered as a fixed dose. Patients should make all attempts to take FT-2102 capsules at the same time on scheduled dose days. Capsules may be taken with 240 mL of water. Capsules should be ingested at least 2 hours after a meal or at least 30 minutes prior to their next meal. Guidance on the timing of FT-2102 capsule ingestion relative to meals may be modified by the Sponsor based on the clinical experience with FT-2102.

In case of BID dosing, FT-2102 should be taken every 12 hours with a minimum of 8 hours between doses.

If a patient vomits at any time after dosing, the dose of FT-2102 should not be re-administered.

Doses of FT-2102 that are omitted for AEs or for any other reason should not be replaced or made up at the end of the dosing period.

When administered in combination with azacitidine, with the exception of C1D1 and C2D1 (when PK sampling is performed), it is recommended that FT-2102 should be administered first on the days when both FT-2102 and azacitidine are given.

The site personnel will train the patients and their caregivers on procedures for drug administration. The pharmacist or study nurse will provide the patients with the correct amount of drug for the subsequent dosing period. Patients will be supplied with the correct amount of capsules for the number of doses to be taken prior to the next scheduled visit.

5.2.2 Azacitidine

Unreconstituted vials of azacitidine must be stored according to storage conditions provided in the VIDAZA® package insert.

Please see pharmacy manual for reconstitution guidelines.

Azacitidine will be administered per SOC at a starting dose of 75 mg/m^2. The recommended dosing schedule for azacitidine is daily × 7 days consecutively (via subcutaneous injection or intravenous infusion), but a 48-hour dose interruption for weekends or holidays is allowed. Azacitidine is to be administered beginning on C1D1 and then Day 1 of each subsequent 28-day treatment cycle. Alternate schedules for the start of azacitidine administration (e.g., beginning on Day 8 of each treatment cycle) may be accepted when clinically indicated.

5.2.3 Cytarabine

Vials of Cytarabine 20 mg/mL Injection must be stored according to the storage condition provided in the package insert. Patients enrolled in the Phase 1 combination cohort of cytarabine + FT-2102 will be treated at a flat dose of 20 mg BID of cytarabine given SC for 10 days every 28-day cycle.

5.3 Drug Accountability and Return of Study Supplies

The Investigator will keep a record of the dates and amounts of study drug received, the amount dispensed to study patients, and the amount unused.

Additionally, patients will be asked to record their dosing in a patient diary.

Drug accountability may be recorded on the appropriate electronic case report form (eCRF) page and on a separate Drug Disposition Record. Returned and/or unused drug should be maintained per institutional policy in a secure location until the Sponsor orders it to be destroyed.

5.4 Concomitant Medications

5.4.1 Allowed Medications

Concomitant medications can be administered at the Investigator's discretion according to standard practice during the treatment period. Necessary supportive measures for optimal medical care will be given throughout the study.

Patients who enroll in the study with leukocytosis at baseline or develop leukocytosis after initiation of therapy may receive hydroxyurea. Suggested guidelines for administering hydroxyurea are as follows:

- For a WBC 10 – 50 x 10^9/L consider administering hydroxyurea 500 mg four times a day
- For a WBC > 50 x 10^9/L consider administering hydroxyurea 1000 mg four times a day
- Hydroxyurea should be tapered/discontinued when WBC count is < 10 x10^9/L

Patients who enroll in the study requiring CNS prophylaxis due to prior CNS involvement and remain asymptomatic may receive intrathecal chemotherapy at the discretion of the investigator. Patients may receive premedication for nausea and/or vomiting at the discretion of the investigator.

Patients may receive antimicrobial treatment or prophylaxis at the discretion of the investigator.

All concomitant medications and supportive therapy administered, starting the first day prior to the first dose and until 28 days after the last dose of FT-2102, must be recorded on the appropriate eCRF page.

5.4.1.1 Concomitant Medications to Use with Caution

Co-administration of FT-2102 with strong CYP3A4 inducers significantly reduces FT-2102 systemic exposure, therefore co-administration is not recommended and investigators should consider alternative medications.

FT-2102 exhibits CYP3A4 induction potential in vitro and may impact the PK of co-administered sensitive CYP3A4 substrates through increased clearance. Medications that are sensitive substrates of CYP3A4 should not be used while taking FT-2102.

If the patient's clinical condition requires a medication of concern, please discuss with the Medical Monitor. Refer to Appendix 9 for a list of strong CYP3A4 inducers and sensitive CYP3A4 substrates.

Additional information can be found at:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1

5.4.2 Prohibited Medications

No other investigational medicinal products will be allowed during this study.

5.4.3 Anticancer Therapy

No concomitant anticancer therapy with the exceptions (hydroxyurea or CNS prophylaxis) noted above, will be allowed during this study.

5.5 Precautions

5.5.1 Differentiation Syndrome

Differentiation syndrome has been observed in patients participating in this ongoing study and has also been reported in patients with AML/MDS receiving other therapies targeting IDH1/2 mutations (Birendra et al. 2016; Fathi et al. 2018) or receiving azacitidine (Laufer and Roberts 2015).

Differentiation syndrome can be defined by the presence of any of the following symptoms: unexplained fever, cough, fast weight gain of more than 10 pounds (5 kg) within a week, bone pain, dizziness or feeling lightheaded, respiratory distress or shortness of breath, interstitial pulmonary infiltrates, pleural or pericardial effusion, swelling of arms & legs and swelling around the neck, groin or underarm with or without hyperleukocytosis (Frankel et al. 1992; Montesinos et al. 2009). No single sign or symptom may be considered per se as diagnostic of the syndrome. However, given the life-threatening character of a full-blown (overt) syndrome, it is recommended that the prophylactic and therapeutic measures indicated below are undertaken at the earliest manifestations of suspected differentiation syndrome (e.g., unexplained respiratory distress).

- Temporary discontinuation of FT-2102 (and azacitidine where indicated) for a minimum of three days;
- Prompt initiation of dexamethasone, 10 mg/12 hrs IV until disappearance of symptoms and signs, and for a minimum of three days;
- Furosemide, supportive measures and hemodynamic monitoring when clinically required.

As soon as the symptoms and the patient's clinical condition improve, and after a minimum of three days, treatment with FT-2102 may be resumed. In case of reappearance of symptoms, FT-2102 should again be held. Resumption of FT-2102, if indicated, should be reduced one dose level for a minimum of the first 7 days after the disappearance of the differentiation syndrome. Thereafter, in absence of worsening of the previous toxicity, FT-2102 can be resumed at full dosage.

Where indicated, as soon as the symptoms and the patient's clinical condition improve, and after a minimum of 3 days, treatment with azacitidine may be reinstituted at ≤ standard dosing and/or delayed further at the investigator's discretion. No dose modifications are required for LDAC.

5.5.2 Leukocytosis

Rapid myeloid proliferation, presenting as leukocytosis has been observed with other IDH inhibitors in the absence of clinical manifestations of differentiation syndrome. In the absence of differentiation syndrome, and unless clinically indicated, leukocytosis does not require dose interruption and should be managed by hydroxyurea as per Section 5.4.1.

5.5.3 Hepatic Injury

Adverse events potentially associated with hepatic dysfunction have been reported in approximately 20% of patients receiving FT-2102 to date. As such, adverse events potentially associated with liver injury have been identified as Adverse Events of Special Interest (AESI). AESI, as defined in Section 7.2.4, regardless if serious or non-serious, must be reported to Forma Therapeutics Pharmacovigilance within 24 hours of knowledge of event as described in Section 7.2.4.

Patients should be monitored for any new or unusual symptoms suggestive of liver injury unrelated to the patient's primary malignancy. Symptoms may include anorexia, nausea, fatigue, right upper abdominal discomfort or vomiting, dark urine or jaundice. In the event of the development of any new clinical signs or symptoms of hepatic dysfunction, the following clinical investigation is recommended with additional action based upon the patient's clinical presentation and at the treating investigator's discretion.

a. Evaluation of international normalized ratio/prothrombin time (INR/PT), albumin, total bilirubin, direct and indirect bilirubin, amylase, lipase, AST, ALT, gamma glutamyl transpeptidase, complete blood count with differential and alkaline phosphatase

If there is evidence of new liver injury, the following actions should occur:

a. Report the AE per Section 7.2.4
b. Consider obtaining FT-2102 serum levels if aberrant dosing is suspected
c. Obtain tests for viral and other infectious etiologies of hepatitis (including hepatitis A, B, C, D and E) and tests for autoimmune hepatitis
d. Consider diagnostic imaging (hepatic ultrasound or MRI) and hepatic biopsy if the patient's clinical status permits
e. Obtain detailed history of symptoms and concurrent or prior disease, concomitant medications including herbal and dietary supplements, alcohol use, recreational drugs (e.g., cannabidiol or tetrahydrocannabinol) and special diets
f. Review medical history to include non-alcoholic steatohepatitis (fatty liver), cardiovascular disease, diabetes, alcoholism or autoimmune disease
g. Evaluate and discontinue if feasible, all hepatic injury-inducing concomitant medications (prescription and over-the-counter) and other hepatic injury-inducing agents (e.g., ethanol)
h. Consider gastrointestinal or hepatology consult

i. Frequent monitoring of AST, ALT, alkaline phosphatase, albumin, INR/PT, and total bilirubin should be initiated. Frequency would be, at minimum, twice per week until asymptomatic and the patient has returned to baseline or Grade 1 toxicity.

Restarting FT-2102 after suspected liver injury:

a. Once the AE returns to Grade 0-1 or baseline, resume treatment with FT-2102 at 150 mg once daily (see Table 8).
b. For the next 28 days, while reduced dosing at 150 mg once daily, AST, ALT and total bilirubin should be monitored at minimum twice per week for the first 2 weeks and then weekly if no recurrence of elevations are observed.
c. If the AE recurs at 150 mg once daily, the patient will be discontinued from study treatment (see Section 6.8.2).
d. If after a minimum of 28 days of 150 mg once daily, the AST, ALT and total bilirubin have not elevated to Grade 2 or greater and no other symptoms, then FT-2102 may be re-escalated to the dose level prior to event.
e. Frequent monitoring (at least twice per week) is required upon re-escalation, and may be decreased after patient has been on the escalated dose for at least 28 days without an increase in the AST, ALT and total bilirubin.

Patients on active treatment with FT-2102 should be informed to promptly notify study staff if they develop any clinical symptoms of jaundice and to avoid personal habits (excessive ethanol consumption, over-the-counter hepatic injurious medications, herbal medications [e.g., cannabidiol or comparable products]) that may cause additional risk of hepatic injury.

5.5.4 Phototoxicity

A phototoxic potential was demonstrated for FT-2102 in a standard *in vitro* assay system. Until the photosafety of FT-2102 has been adequately demonstrated *in vivo*, phototoxicity risks in the clinical setting will be managed by the use of light-protective measures. Patients should be instructed to avoid extensive sun exposure, phototherapy, or use of a tanning salon within a prudent amount of time prior to and following trial participation.

5.6 Childbearing Potential

For all patients of childbearing potential, all methods of contraception, including abstinence, must be in use from the time of consent through the final study visit, and for 90 days after the last dose of study drug. Patients who are not sexually active during the Screening Period must agree to the contraceptive requirements if they become sexually active with a partner of the opposite sex during the study and for 90 days after the last dose of study drug. Unique situations that may not fall within these specifications may be discussed with the Forma Therapeutics Medical Monitor on an individual basis.

Female patients will be considered of childbearing potential after the onset of their first menstrual period. Female patients who are documented as being of nonchildbearing potential

(postmenopausal or having undergone surgical sterilization) are exempt from this requirement. Female patients will be considered postmenopausal if they have had 12 months of consecutive spontaneous amenorrhea or less than 12 months of consecutive spontaneous amenorrhea and a serum FSH level > 40 mIU/mL at Screening. Female patients will be considered surgically sterile if they are post-hysterectomy, 6 months post-surgical bilateral oophorectomy, or 6 months post-tubal ligation.

5.6.1 Contraception Guidelines

Acceptable methods of contraception under this protocol are listed below. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Male patients who can father a child must agree to use one highly effective method of contraception, which includes:

- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the patient.
- If a male patient confirms that his female partner(s) is not of childbearing potential (i.e., postmenopausal or post-surgical sterilization, as defined above) or is using a highly effective method of contraception, this is acceptable as the only means of contraception.

  Examples of highly effective methods of contraception for male patients' female partner(s) include:
  - Hormonal contraceptives
  - Intrauterine device (IUD)

Male patients with documented infertility or surgical sterilization (performed at least six months before the first dose of study drug) are exempt from the contraception requirement. Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens on ultrasound before the first dose of study drug (Day 1).

Female patients who are considered of childbearing potential must agree to use a highly effective method of contraception, which may include:

- IUD
- Abstinence: abstinence can be used, when in line with the preferred and usual lifestyle of the patient.
- If a female patient confirms that her male partner(s) has been confirmed to be clinically sterile, this method is acceptable as the only means of contraception.

Hormonal contraceptives are not considered an effective method of birth control for female patients participating in this study. Male condoms with female condoms should not be used together.

5.6.2 Guidance Against Donating Sperm or Ova

Male patients are prohibited from donating sperm and female patients of childbearing potential are prohibited from donating ova during the study and for 90 days after the final dose of study drug.

6 STUDY PROCEDURES

6.1 Measurements and Evaluations

See Appendix 1 and Appendix 2 for a detailed study Schedule of Events, including measurements and evaluations for the entire study period (Screening to Follow-up) presented in tabular form.

For Protocol Version 7/ Amendment 6, a reduced Schedule of Events has been introduced for all ongoing patients receiving treatment at the time of the amendment (see Appendix 1) and a new Schedule of Events has been added for patients enrolled after Protocol Version 7/ Amendment 6 (eg, patients that transfer from Cohort 1 to Cohort 3 or Cohort 6) (see Appendix 2).

6.1.1 Pre-screening

Sites that do not perform IDH1 mutation testing as part of their SOC may have the option to send pre-screening patients' samples for central laboratory IDH1 mutation detection before study enrollment.

6.1.2 Informed Consent

Prior to the initiation of any study-specific procedures or assessments, the Investigator or designee must provide to each patient a complete explanation of the purpose and methods (procedures and assessments) of the study. Subsequently, the patient must receive and sign a copy of both the Informed Consent Form (ICF) and the Authorization of Use and Disclosure of Protected Health Information (PHI) approved by the study site Institutional Review Board (IRB)/ ethics committee (EC). Once informed consent has been obtained, the eligibility of the patient will be determined, and Screening Period assessments can then be performed.

6.1.3 Screening Period (Within 14 Days Prior to Day 1)

The following evaluations will be performed to assess the patient's eligibility for the study per schedule of events:

- Complete medical history (including surgical and cardiac history)
- Leukemia and/or MDS medical history with treatment history
- Physical examination
- Height and weight
- Concomitant medication assessment
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Serum pregnancy test (for nonsterile women of childbearing potential)
- 12-lead ECG in triplicate (should be conducted within a 10-minute period)
    - Performed as clinically indicated for patients enrolled after Protocol Version 7/ Amendment 6

- Clinical serum chemistries
- CBC with differential and platelet count
- Bone marrow aspirate and peripheral blood (for clinical purposes), refer to the laboratory manual for details of sample collection and timing
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6 if collected at End of Treatment visit prior to roll-over
- Local IDH1m confirmation (this may have occurred > 28 days prior)
- Coagulation parameters (PT and PTT)
- Blood sample collection for PD analysis (See Section 6.5 for PD sampling times)
- Urinalysis
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- AE monitoring
- EQ-5D-5L QOL (any time prior to first dose) (Phase 2 only)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6

6.1.4 Cycle 1, Day 1

All procedures to be performed predose, with the exception of postdose PK/PD sample collection and ECG. Following completion of predose procedures, patients will receive their first dose of FT-2102.

Note: Patients will receive only a single dose of study drug (single-agent arm and combination arm) on Cycle 1 Day 1:

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Physical examination
- Serum or urine pregnancy test (for nonsterile women of childbearing potential)
- 12-lead ECG (predose [Phase 1 and 2], and 2 hr, 4 hr, 8 hr postdose [Phase 1 only]) in triplicate should be conducted within a 10-minute period
    - As clinically indicated for patients enrolled after Protocol Version 7/ Amendment 6
- Clinical serum chemistries
- CBC with differential and platelet count
- Urinalysis
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6

- 24-hour Holter monitoring (see manual for details) at all centers in the United States (US) and select centers outside of the US (ex-US)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6

Day 1 testing, with the exception of PK/ PD collections and ECG (including Holter) assessments, may be done within 72 hours prior to the Day 1 visit and do not need to be repeated if performed during Screening within the allotted window.

Note: Patients taking BID dose will be instructed to not administer their 2nd dose of FT-2102 on C1D1.

6.1.5 Cycle 1, Day 2 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures will be performed at this visit:

- Concomitant medication assessment
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times); to occur prior to dosing and at or near the same time as collection at the previous study visit (i.e., approximately 24 hours after the first dose of study drug was administered)
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times); to occur prior to dosing and at or near the same time as collection at the previous study visit (i.e., approximately 24 hours after the first dose of study drug was administered)
- Completion of 24-hour Holter monitoring (pre-dose) at all centers in the US and select centers ex-US

Note: Patients receiving FT-2102 on a BID schedule should be instructed to take a second dose of study drug later in the day.

6.1.6 Cycle 1, Day 5 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- CBC with differential and platelet count
- Clinical serum chemistries

6.1.7 Cycle 1, Day 8 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose:

- Concomitant medication assessment

- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Symptom-directed physical examination
- 12-lead ECG in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries
- CBC with differential and platelet count
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)

Day 8 testing, with the exception of PK/PD and ECG collections, may be done within 24 hours prior to the Day 8 visit.

6.1.8 Cycle 1, Day 12 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- Clinical serum chemistries
- CBC with differential and platelet count

6.1.9 Cycle 1, Day 15 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose:

- Concomitant medication assessment
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Symptom-directed physical examination
- 12-lead ECG in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries
- CBC with differential and platelet count
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)

Day 15 testing, with the exception of PK/PD and ECG collections, may be done within 48 hours prior to the Day 15 visit.

6.1.10 Cycle 1, Day 19 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- Clinical serum chemistries

- CBC with differential and platelet count

6.1.11 Cycle 1, Day 22 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose:

- Concomitant medication assessment
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Symptom-directed physical examination
- 12-lead ECG in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries
- CBC with differential and platelet count
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)

Day 22 testing, with the exception of PK/PD and ECG collections, may be done within 48 hours prior to the Day 22 visit.

6.1.12 Cycle 1, Day 26 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- Clinical serum chemistries
- CBC with differential and platelet count

6.1.13 Cycle 2, Day 1 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose, with the exception of postdose PK/PD sample collection and ECG:

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Symptom-directed physical examination
- Serum or urine pregnancy test for female patients of childbearing potential
- 12-lead ECG (predose [Phase 1 and 2], and 2 hr, 4 hr, 8 hr postdose [Phase 1 only]) all timepoints in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries

- CBC with differential and platelet count
- Coagulation parameters (PT and PTT)
- Urinalysis
- AE monitoring
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- **Note**: A 72-hour wash-out post C2D1 dosing will be requested from all patients participating in the dose-expansion stage. After the C2D1 FT-2102 AM dose, patients will be asked to refrain from taking FT-2102 until the AM of C2D4.
- Bone marrow aspirate or biopsy for disease assessment/ cancer-associated mutation analysis (for an early disease assessment in patients with resolution of peripheral blasts)
- 24-hour Holter monitoring (see manual for details) at all centers in the US and select centers ex-US.
- EQ-5D-5L QOL (Phase 2 only)

Cycle 2 Day 1 testing, with the exception of PK/PD and ECG (including Holter), collections may be done within 48 hours prior to the Day 1 visit.

6.1.14 Cycle 2, Day 2 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

Applicable for all patients participating in the Phase 1 dose-expansion stage and the subset of patients participating in 24-hour Holter monitoring (see manual for details):

- Concomitant medication assessment
- AE monitoring
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- Completion of 24-hour Holter monitoring (pre-dose) at all centers in the US and select centers ex-US

6.1.15 Cycle 2, Day 4 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

Applicable for all patients participating in the Phase 1 dose-expansion stage:

- Concomitant medication assessment
- AE monitoring
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
  Note: Collect prior to re-starting FT-2102

6.1.16 Cycle 2, Day 8 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedure should be performed (local laboratory testing allowed):

- Clinical serum chemistries
- CBC with differential and platelet count

6.1.17 Cycle 2, Day 15 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose:

- Concomitant medication assessment
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- Symptom-directed physical examination
- 12-lead ECG in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries
- CBC with differential and platelet count
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)

Cycle 2 Day 15 testing, excluding PK and PD collections, may be done within 48 hours prior to the Day 15 visit.

6.1.18 Cycle 2, Day 22 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- CBC with differential and platelet count
- Clinical serum chemistries

6.1.19 Cycle 3, Day 1

All procedures to be performed predose:

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Symptom-directed physical examination
- Serum or urine pregnancy test for female patients of childbearing potential
- 12-lead ECG in triplicate should be conducted within a 10-minute period

    - As clinically indicated for patients enrolled after Protocol Version 7/ Amendment 6
- Clinical serum chemistries
- CBC with differential and platelet count
- Bone marrow aspirate or biopsy for disease assessment and cancer-associated mutation analysis:
    - Required on Cycle 3 Day 1 in any patient who did not undergo a Cycle 2 Day 1 bone marrow aspirate (BMA) or biopsy (Bx) assessment
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- Urinalysis (if medically indicated)
- AE monitoring
- Blood sample collection for PK analysis (see Section 6.4 for PK sampling times)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- Blood sample collection for PD analysis (see Section 6.5 for PD sampling times)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6
- EQ-5D-5L QOL (Phase 2 only)
    - Not applicable for patients enrolled after Protocol Version 7/ Amendment 6

Cycle 3, Day 1 testing, with the exception of PK/PD, may be done within 72 hours prior to the Day 1 visit.

6.1.20 Cycle 3, Day 15 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

The following procedures should be performed (local laboratory testing allowed):

- Clinical serum chemistries
- CBC with differential and platelet count

6.1.21 Cycle 4, Day 1 (Not Applicable for Patients Enrolled after Protocol Version 7/ Amendment 6)

All procedures to be performed predose:

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Symptom-directed physical examination
- Serum or urine pregnancy test for female patients of childbearing potential
- 12-lead ECG in triplicate should be conducted within a 10-minute period
- Clinical serum chemistries
- CBC with differential and platelet count

- Bone marrow aspirate or biopsy for disease assessment and cancer-associated mutation analysis:
    - Day 1 on any cycle where response assessment is indicated per Response assessment guidelines (see Section 4.3)
- Urinalysis (if medically indicated)
- AE monitoring
- Blood sample collection for PK analysis Day 1 of every cycle (see Section 6.4 for PK sampling times)
- Blood sample collection for PD analysis Day 1 of every cycle (see Section 6.5 for PD sampling times)
- EQ-5D-5L QOL (Phase 2 only)

Cycle 4: Day 1 testing, with the exception of PK/PD, may be done within 72 hours prior to the Day 1 visit.

6.1.22 Cycle 5 and Beyond, Day 1 (Every Other Cycle)

Beginning with Cycle 5, patients will return to the clinic every other cycle.

All procedures to be performed predose:

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- 12-lead ECG as clinically indicated
- ECOG performance status
- Symptom-directed physical examination
- Serum or urine pregnancy test for female patients of childbearing potential
- Clinical serum chemistries
- CBC with differential and platelet count
- Bone marrow aspirate or biopsy for response assessment
    - For patients with AML: Every 6 cycles unless there is an indication of relapse/progression
    - For patients with MDS: As clinically indicated
    - For patients enrolled in Phase 2 Cohort 2: Only if there is a suspicion of relapse
- AE monitoring

Cycle 5 and beyond (every other cycle): Day 1 testing may be done within 72 hours prior to the Day 1 visit.

6.1.23 End of Treatment Assessments

The following assessments should be performed within 7 days from decision to discontinue treatment with FT-2102 (vs. discontinuation from the entire study, as detailed in Section 8.2):

- Concomitant medication assessment
- Weight
- Vital signs (temperature, blood pressure, pulse rate, and respiratory rate)
- ECOG performance status
- Physical examination
- Serum or urine pregnancy test for female patients of childbearing potential
- 12-lead ECG as clinically indicated
- Clinical serum chemistries
- CBC with differential with platelet count
- Bone marrow aspirate or biopsy (for disease assessment) as clinically indicated
- Urinalysis if medically indicated
- AE monitoring

If the patient had any of these assessments within the previous 2 weeks (4 weeks for bone marrow aspirate or biopsy), then these assessments need not be repeated.

6.1.24 Safety Follow-up Visit/Interview

All AEs will be followed for 28 days after administration of last dose of study drug or until resolution or stabilization as documented by physical examination or appropriate laboratory results. If subsequent anticancer therapy is initiated earlier, this visit or contact should occur before the initiation of subsequent anticancer therapy. The data should be documented on the appropriate eCRF page.

6.1.25 Disease Response Follow-up

Patients who discontinue study treatment for reasons other than treatment failure and have not withdrawn consent from overall study participation, should continue to be followed for disease response assessments until the time of disease progression/relapse or the initiation of a new treatment regimen. Patients who have stopped FT-2102 treatment for HSCT should continue to be followed until disease progression/ relapse. This information should be documented on the appropriate eCRF page.

6.1.26 Survival Follow-up

After a patient discontinues or completes study treatment, the study site may be requested to contact the patient approximately every 3 months to collect survival status and data pertaining to any other alternative anti-neoplastic therapy. Patients enrolled in the Phase 1 dose-escalation/

dose-expansion stages may have survival follow-up performed for up to 12 months from C1D1 or 28 days after administration of last dose of drug (whichever is longer). Patients enrolled in the Phase 2 cohorts may have survival follow-up for up to 36 months from C1D1 or 28 days after administration of last study drug (whichever is longer).

6.2 Safety

Safety variables to be assessed include: AEs, clinical laboratory tests, vital signs measurements, physical examination findings, and ECG readings (see manual for details of Holter monitoring procedures).

6.2.1 Data Monitoring Committee

Close monitoring of serious safety events as they are reported is conducted by the medical monitor. Serious and non-serious adverse event review is conducted regularly by the medical monitor through monthly listing review. Safety events are also reviewed during regular study conduct meetings between the medical monitor, the clinical team, pharmacovigilance, and the participating investigators.

These study-conduct meetings during the Phase 1 component of this trial include bi-weekly internal review meetings to monitor study progress/safety events and bi-weekly teleconferences with investigators. For the Phase 2 component of the trial monthly meetings with investigators are held.

Periodic safety reviews by Forma's internal DMC, consisting of the clinical study team, pharmacovigilance, and medical monitors not directly involved in the conduct of Study 2102-HEM-101, also occur.

This internal DMC meets at least bi-annually to review safety listings and on an ad hoc basis in response to new safety signals to rapidly assess overall risk to participants. The outcome of these internal DMC meetings, when relevant, is quickly communicated to study investigators so they may share current risk information with their patients and collect updated informed consent forms, if appropriate.

6.3 Bone Marrow Aspirate and/or Biopsy

A bone marrow aspirate for clinical purposes should be obtained from each patient prior to initiating study treatment (baseline) and while on treatment at the time of response assessment (as per Section 4.3).

Bone marrow materials prepared according to the guidelines in the laboratory manual will meet specifications to enable central testing (where indicated) for mutational analysis (including confirmation of presence of IDH1-R132 mutation). Bone marrow biopsy may be used for on-study disease assessment when bone marrow aspirate is a dry tap.

Refer to the laboratory manual for additional instructions on collecting and processing bone marrow aspirates and biopsies.

6.4 Pharmacokinetics

Note: As of Protocol Version 7/ Amendment 6, PK samples are no longer being collected.

The plasma PK collections will be performed as detailed in Table 4. Blood samples will be collected. The actual time of blood collection must be documented in the respective form, and any deviations outside of the time limits must be commented upon. The scheduled blood sampling times will be used for the PK analysis; however, any deviations outside the limits (real times) are relevant and the data sets will be adjusted for the PK evaluations and the real times will be used.

A laboratory manual will be provided with instructions for collecting and processing of the samples.

Table 4 Pharmacokinetic Sampling Times: FT-2102

Cycle	Day	Sample	Collection Times[a]	Phase 1 Patients	Phase 2 Patients (24 hr Holter Monitoring)	Phase 2 Patients (No 24 hr Holter Monitoring)
1	1	1	Predose	X	X	X
		2	30 minutes after dosing (+/- 5 minutes)	X	X	
		3	1 hr after dosing (+/- 5 minutes)	X	X	
		4	2 hr after dosing (+/- 15 minutes)	X	X	
		5	4 hr after dosing (+/- 15 minutes or 2 hours[b])	X	X	X
		6	8 hr after dosing (+/- 30 minutes)	X	X	
	2	1	Predose	X	X	
	8, 15, and 22	1	Predose	X		
2	1	1	Predose	X	X	X
		2	30 minutes after dosing (+/- 5 minutes)	X	X	
		3	1 hr after dosing (+/- 5 minutes)	X	X	
		4	2 hr after dosing (+/- 15 minutes)	X	X	
		5	4 hr after dosing (+/- 15 minutes)	X	X	
		6	8 hr after dosing (+/- 30 minutes)	X	X	
	2	1	24 hrs after C2D1 dosing (+/- 2 hrs)	X	X	
	4	1	Predose [72 hrs after C2D1 dosing (+/- 4 hrs)]	X[c]		
	15	1	Predose	X		
3 and 4	1	1	Predose	X	X	X
Random	TBD	1	Collected in the setting of potential treatment-related AE	X	X	X

[a] PK sampling times are specific for FT-2102.

[b] +/- 15 minutes for Phase 1/ Phase 2 Holter Monitor and +/- 2 hours for Phase 2.

[c] Performed in patients participating in the dose-expansion stage only.

Plasma concentration data will be used to determine the following PK parameters:

- AUC Area under the concentration curve
- C_{max} Maximum plasma concentration
- T_{max} Time to maximum plasma concentration
- $t_{1/2}$ Terminal elimination half life
- CL/F Total body clearance
- V_d/F Apparent volume of distribution

6.5 Pharmacodynamics

Note: As of Protocol Version 7/ Amendment 6, PD samples are no longer being collected.

Peripheral blood samples for exploratory PD assessments will be collected at the specified times detailed in Table 5. Blood samples will be collected. The actual time of blood collection must be documented in the respective form and any deviations outside of the time limits must be commented upon.

The scheduled blood sampling times will be used for the PD biomarker analysis; however, any deviations outside the limits (actual times) are relevant and the data sets will be adjusted for the PD evaluations and the actual times will be used.

A laboratory manual will be provided with instructions for collecting and processing of the samples.

Table 5 Pharmacodynamic Sampling Times: FT-2102 (Single Agent) and FT-2102 plus Azacitidine or Low-Dose Cytarabine (Combination)

Cycle	Days	Sample	Collection Times	Phase 1 Patients	Phase 2 Patients (24 hr Holter Monitoring)	Phase 2 Patients (No 24 hr Holter Monitoring)
Screening	NA	**1**	Predose	X		
1	**1**	**1**	Predose	X	X	X
	2	**1**	Predose	X		
	8	**1**	Predose	X		
	15	**1**	Predose	X		
	22	**1**	Predose	X		
2	**1**	**1**	Predose	X	X	X
	2[a]	**1**[b]	--	X		
	4[a]	**1**[b]	Predose	X		
	15	**1**[b]	Predose	X		
3 and 4	**1**	**1**	Predose	X	X	X

[a] Collected in dose-expansion patients during C2D2 and at the end of 72 hr FT-2102 washout (C2D4) (see Schedule of Events in Appendix 1).

[b] Not required in Phase 2.

6.6 Mutational Analysis

Note: As of Protocol Version 7/ Amendment 6, samples for mutational analysis are no longer being collected.

Bone marrow aspirate and peripheral blood samples for exploratory assessments of cancer-associated mutations and/or genetic alterations will be collected as follows:

A bone marrow aspirate sample will be collected during the Screening period, prior to Cycle 1 Day 1. If the patient had a bone marrow aspirate performed within 28 days of Cycle 1 Day 1 and there is sufficient sample available for analysis, it does not need to be repeated.

At any time while on treatment, if a patient undergoes a bone marrow aspirate or biopsy sample collection for response assessment, material will be requested for cancer-associated mutations analysis (refer to Section 4.3 and Section 6.3 for timepoint details).

Peripheral blood samples will be collected at Screening and at each timepoint that a bone marrow aspirate or biopsy is obtained.

See the laboratory manual provided for details of the specific analyses and instructions on collecting and processing of these samples.

Note: Pretreatment bone marrow aspirate and peripheral blood samples for retrospective confirmation of IDH1m by the central assay is mandatory for efficacy evaluable (EE) population definition, and not an exploratory assessment.

6.7 Outcome Research Assessment

Note: As of Protocol Version 7/ Amendment 6, quality of life assessments are no longer being performed.

Throughout the clinical trial period, patients will be asked about their quality of life via the Quality of Life questionnaires EQ-5D-5L.

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group to describe and value health related quality of life. The instrument comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated by the patients on a 5 point scale as having 'no problems' (a score of 1), 'slight problems (a score of 2), 'moderate problems', (a score of 3), 'severe problems', (a score of 4) and 'extreme problems', (a score of 5) based on descriptive examples: the scores are not intended to be summed. Present overall state of health is also to be rated on a vertical visual analogue scale (approximately 20cm in length) from 0 to 100 (the higher the number the better quality of life.

The EQ-5D-5L will be performed at screening (any time prior to first dose) and then monthly on Day 1 of Cycles 1 to 4 (completed prior to all other D1 procedures) for all Phase 2 patients.

Patients should self-complete the EQ-5D-5L and return to the site. Data will then be entered into the patient's eCRF.

6.8 Dose Modifications

6.8.1 FT-2102 Dose Modifications

Patients participating in the dose-escalation stage who are receiving a dose of FT-2102 that is one level below an established safe dose may be considered for intrapatient dose escalation if they have not experienced a protocol-defined dose limiting toxicity at the lower dose level, and pending a consultation between the Investigators and Medical Monitor.

If a patient has an AE that is judged by the Investigator as related to study drug (i.e., assessed as unrelated to the underlying disease, intercurrent illness, or concomitant medications), then dose modifications can be made according to the guidelines in Table 6. Dose modification guidelines for liver function test (LFT) abnormalities are presented in Table 7. Dose reduction guidelines are presented in Table 8.

Deviations from these guidelines (e.g., drug interruption for a Grade 2 pleural effusion) may occur if agreed upon by the Principal Investigator and Medical Monitor. There should be no attempt to make up doses omitted due to toxicity.

Table 6 FT-2102 Recommended Dose Modifications for Adverse Events Unrelated to Liver Function Abnormalities

Severity of Adverse Events	Dose Modifications for FT-2102 [c]	
	Non-Hematologic	**Hematologic**
Grade 1	Continue treatment at the same dose	Continue treatment at the same dose
Grade 2	Continue treatment at the same dose. If dose interruption is clinically indicated, resume dosing at same dose level after recovery to ≤ G1	Continue treatment at the same dose
Grade 3	Hold treatment until recovery to ≤ G1 or baseline, whichever is worse [a], then resume at the next lower dose level. Contact Medical Monitor if resumption of FT-2102 at full dose is clinically indicated.	Continue treatment at the same dose. If dose interruption is clinically indicated, resume dosing at same dose level after recovery to ≤ G2
Grade 4	Permanently discontinue treatment [b]	Hold treatment until recovery to ≤ G2 or baseline, whichever is worse, then resume at the next lower dose level. Contact Medical Monitor if resumption of FT-2102 at full dose is clinically indicated.

AE = adverse event.

[a] In the event of Grade 3 nausea, vomiting, diarrhea, or rash, the patient can continue at the same dose if the patient is responsive to treatment measures within 72 hr.

[b] A patient with a Grade 4 AE may resume treatment at the next lower dose level if the AE recovers to Grade 0-1 or baseline and if in the opinion of the Investigator and Sponsor, the patient can be monitored for recurrence of AE.

[c] Dose modification may be more or less conservative at the Investigator's discretion and after consultation with the medical monitor.

Table 7 FT-2102 Recommended Dose Modifications for Liver Function Test Abnormalities

Laboratory Abnormality	Action to be Taken with FT-2102
AST or ALT or total bilirubin is Grade 3	Hold FT-2102
AST or ALT is > 3 times the ULN and patient has signs and symptoms of a hypersensitivity reaction not related to underlying disease [e.g., fatigue, nausea, vomiting, RUQ pain or tenderness, fever, rash and/or eosinophilia (>5%)]	Hold FT-2102
For patient with elevated AST or ALT or total bilirubin at baseline: AST or ALT > 2 times baseline AND > 3.0 times ULN OR AST or ALT > 8.0 times ULN- whichever is lower- combined with total bilirubin > 2 times baseline AND > 2 times ULN	Hold FT-2102
AST or ALT is > 3 times the ULN and the total bilirubin is > 2 times ULN and Alkaline phosphatase < 2 times ULN in the absence of a clear alternative explanation	Permanently discontinue FT-2102
AST or ALT or total bilirubin is Grade 4	Permanently discontinue FT-2102

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RUQ = right upper quadrant; ULN = upper limit of normal.

6.8.2 FT-2102 Recommended Dose Reductions

A dose may be withheld up to 28 days (up to 14 days for Cycle 1 only) for toxicity. Doses withheld for > 28 days (> 14 days for Cycle 1 only) may result in discontinuation from the study, unless approved by the medical monitor.

In the Phase 1 dose escalation part of the study: Dose reductions in Cycle 1 are allowed only after a DLT and not below the 150 mg QD.

Recommended dose reductions for all AEs including those associated with LFT abnormalities are outlined in Table 8.

Table 8 Recommended FT-2102 Dose Reduction Levels

Starting Dose	Reduction Level -1
150 mg BID[a]	150 mg QD

a. Patients currently treated with 100 mg BID can further reduce to 150 mg QD if clinically indicated.

Patients who have a dose reduction due to toxicity may be eligible for a dose increase back to the initial dose if the following criteria are met:

1. Patient has recovered to baseline levels from the toxicity which caused the dose reduction
2. Patient has tolerated the lower treatment dose for > 1 week (or at least 28 days for liver function test abnormality AEs)

Any patient who requires a dose reduction > 1 level below starting dose will be discontinued from the study. Patients who discontinue treatment must be monitored per study procedure and assessment schedule, unless they withdraw consent.

6.8.3 Azacitidine Dose Modifications

Patients enrolled in the combination arm of azacitidine + FT-2102 will be treated at a stable azacitidine dose of 75 mg/m^2/day for 7 days consecutively (via subcutaneous injection or intravenous infusion), but a 48-hour dose interruption for weekends or holidays is allowed. Azacitidine is to be administered beginning on Cycle 1 Day 1 and then Day 1 of each subsequent 28-day treatment cycle. Alternate schedules for the start of azacitidine administration (e.g., beginning on Day 8 of each treatment cycle) is accepted when clinically indicated at the investigator's discretion.

Patients who are unable or unwilling to continue treatment with azacitidine after the first treatment cycle may continue participation in the study taking FT-2102 alone, at the discretion of the investigator. During Cycle 1, in dose escalation cohorts only, patients who do not receive at least 75% of their scheduled dose due to drug toxicity (dose hold) will have that counted towards the criteria for a DLT.

Azacitidine dose adjustment may be more or less conservative per investigator's discretion according to the local institutional guidelines.

6.8.3.1 Azacitidine Dose Adjustment Based on Hematology Laboratory Values

Azacitidine dose modifications based on hematology laboratory values are presented in Table 9.

For patients with baseline (start of treatment) WBC $\geq 3.0 \times 10^9$/L, ANC $\geq 1.5 \times 10^9$/L, and platelets $\geq 75.0 \times 10^9$/L, adjust the dose as shown in Table 9A, based on nadir counts for any given cycle. For patients whose baseline counts are WBC $< 3.0 \times 10^9$/L, ANC $< 1.5 \times 10^9$/L, or platelets $< 75.0 \times 10^9$/L, dose adjustments should be based on nadir counts and bone marrow cellularity at the time of the nadir as shown in Table 9B, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

Table 9 Azacitidine Dose Modifications: Hematology Laboratory Values

A – Baseline WBC $\geq 3.0 \times 10^9$/L, ANC $\geq 1.5 \times 10^9$/L, and platelets $\geq 75.0 \times 10^9$/L				
Nadir Counts		**% Dose in the Next Course**		
ANC ($\times 10^9$/L)	**Platelets ($\times 10^9$/L)**			
< 0.5	< 25.0	50%		
0.5 – 1.5	25.0 – 50.0	67%		
> 1.5	> 50.0	100%		
B – Baseline WBC $< 3.0 \times 10^9$/L, ANC $< 1.5 \times 10^9$/L, or platelets $< 75.0 \times 10^9$/L				
WBC or Platelet Nadir Percent decrease in counts from Baseline		**Bone Marrow Cellularity at time of nadir (%)**		
		30 – 60	15 – 30	< 15
50 – 75		**Percent dose in the next course**		
		100	50	33
> 75		75	50	33

ANC = absolute neutrophil count; WBC = white blood cell (count).

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are > 25% above the nadir and rising. If a > 25% increase above the nadir is not seen by Day 28, counts should be reassessed every seven days. If a 25% increase is not seen by Day 42, then the patient should be treated with 50% of the scheduled dose.

In patients achieving CRi, if the incomplete hematological recovery is considered to be related to azacitidine, dose reduction and treatment interruptions may be considered at the investigator's discretion.

6.8.3.2 Dose Adjustment of Azacitidine Based on Serum Electrolytes and Renal Toxicity

If unexplained reductions in serum bicarbonate levels to < 20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment course. In addition, the laboratory parameters that resulted in the dose delay or reduction should be rechecked twice weekly until they return to baseline or grade 1 level, whichever is worse.

6.8.4 Cytarabine

Patients enrolled in the Phase 1 combination cohort of cytarabine + FT-2102 will be treated at a flat dose of 20 mg BID of cytarabine given subcutaneously (SC) for 10 days every 28-day cycle.

Cytarabine dosing delays and interruptions for adverse events are allowed at the Investigator's discretion.

Patients who are unable or unwilling to continue treatment with LDAC after the first treatment cycle may continue participation in the study taking FT-2102 alone, at the discretion of the investigator. During Cycle 1, patients who do not receive their scheduled dose due to drug toxicity (resulting in dose hold) will have that counted towards the criteria for a DLT.

7 PROCEDURES FOR REPORTING ADVERSE EVENTS

7.1 Adverse Events Definitions

The Investigator will monitor the occurrence of AEs during the course of the study and for 28 days after the administration of the last dose of study drug.

The following definitions of terms are guided by the International Council on Harmonisation and the United States Code of Federal Regulations and are included here verbatim.

Adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.

Serious Adverse Event is any adverse event that results in any of the following outcomes: Death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life-threatening refers to any adverse event that places the patient or subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Associated with the use of the drug means that there is a reasonable possibility that the experience (event) may have been caused by the drug.

Unexpected adverse event means any adverse event, the specificity or severity of which is not consistent with those listed in the current Investigator's Brochure (IB).

7.2 Reporting of Adverse Events

7.2.1 Adverse Events

Refer to Section 6.2.1 for a summary of ongoing safety review during the study, including review of any new Suspected Unexpected Serious Adverse Reactions (SUSARs).

Serious AEs (SAEs) will be collected from the time the patient signs the informed consent form until 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first, and as per Section 7.2.3. Serious AEs will be collected on the Adverse Event eCRF from the time of first dose of study drug until 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first.

Adverse Events of Special Interest (AESI), as defined in Section 7.2.4, should be collected on the AESI Form from the time of first dose of study drug until 28 days after the last dose of study drug and reported to Forma Therapeutics Pharmacovigilance within 24 hours of knowledge of event.

Non-serious adverse events will be collected and reported on the Adverse Event eCRF from the time of the first dose of study drug until 28 days after the last dose of study drug, or until the initiation of an investigational agent or cytotoxic chemotherapy, whichever comes first.

Patients withdrawn from the study because of AEs will be followed by the Investigator until the outcome is determined. When appropriate, additional written reports and documentation will be provided.

All AEs beginning after the last exposure of study drug must be reported to the Sponsor or its designee if the onset of the AE was within 28 days of the last exposure to study drug. All AEs, whether serious or nonserious, that are judged by the Investigator to be at least possibly related to study drug administration must be reported to the Sponsor or its designee regardless of how much time has elapsed since the last exposure to study drug (i.e., beyond 28 days of the last exposure to study drug).

7.2.2 Laboratory Abnormalities

To the extent possible, all new or worsening laboratory abnormalities observed during the course of the study will be included under a reported AE describing a clinical syndrome (e.g., elevated blood urea nitrogen and creatinine in the setting of an AE of "renal failure" or elevated ALT/AST in the setting of an AE of "hepatitis"). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

An abnormal laboratory value that is not already associated with an AE (e.g., symptoms or diagnosis) is to be recorded as an AE only if an action on the study drug or concomitant medication is made as a result of the abnormality, if intervention or management of the abnormality is required, or at the discretion of the Investigator.

Patients experiencing laboratory abnormalities will be assessed and appropriate evaluations performed until all parameters have returned to baseline levels, or are consistent with the patient's then-current physical condition.

7.2.3 Serious Adverse Events

Instructions for reporting Serious Adverse Events are found on Page 4.

A written report of all SAEs and deaths that occur between the signing of the ICF and 28 days after administration of the last dose must be submitted to the IRB/EC and Forma Therapeutics Pharmacovigilance. All SAEs must be reported to Forma Therapeutics Pharmacovigilance within 24 hours for a determination of expedited reporting to the relevant regulatory health authority, as

described in Section 7.5. In all SAE reports, the Investigator will advise whether or not the SAE is judged to be related to study drug administration.

Serious AEs and deaths that occur more than 28 days after administration of the last dose and are not reasonably associated with study drug do not require reporting per the instructions given below. All SAEs that are judged by the Investigator to be at least possibly related to study drug administration must be reported to the Sponsor or its designee regardless of how much time has elapsed since the last exposure to study drug. All nonserious AEs must be communicated to the appropriate IRB/EC and/or reported in accordance with local laws and regulations.

7.2.4 Adverse Events of Special Interest

As described in Section 5.5.3, adverse events potentially associated with liver injury have been identified as AESI. These AESI (regardless if serious or non-serious) include the following:

a. All events of Grade 2 or higher elevations in ALT, AST, or total bilirubin in patients with normal LFTs at baseline; in patients with elevated LFTs at baseline, one Grade shift or higher in ALT, AST, or total bilirubin;
b. Any hepatic adverse event, e.g., acute hepatitis, cholestatic hepatitis, cholestasis, or hepatic insufficiency

AESI occurring from time of first dose through 28 days after last dose must be reported as outlined below:

a. Report to Forma Therapeutics Pharmacovigilance within 24 hours of knowledge of event
b. If the event meets both AESI and SAE criteria, complete both the SAE and AESI form
c. If the event is non-serious, complete the AESI form alone

Relevant forms (AESI, SAE, or both) should be submitted via fax (+1-617-321-4111) or email (safety@formatherapeutics.com) to Forma Therapeutics Pharmacovigilance.

7.2.5 Reporting of Pregnancies

If a patient, or the female partner(s) of a male study patient, becomes pregnant during the course of the study, the Investigator or site personnel must notify Forma Therapeutics Pharmacovigilance (see Page 4 for contact details) within 24 hours of the Investigator or site personnel becoming aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (within 24 hours) must be met.

The Sponsor's representative will provide instructions on how to collect pregnancy information as per the pregnancy reporting guidelines. The pregnancy reporting period begins upon administration of the first dose of FT-2102, and pregnancies will be reported until 90 days after the last dose of FT-2102. A final Pregnancy Report Form should be completed when outcome of the pregnancy is known. Any follow-up information on the outcome of the pregnancy should be forwarded to the Sponsor.

7.2.6 Disease Progression

If progression of the underlying disease (i.e., the condition being treated with study drug) might be reasonably anticipated given the nature and severity of the underlying disease, then progression of the underlying disease per se will not constitute an AE. However, if the progression of the underlying disease meets the criterion for "serious" categorization of AEs (e.g., the underlying disease results in death or hospitalization), then the progression of underlying disease should be reported as an SAE (See Section 7.2.3).

7.2.7 Overdoses

Overdoses during the course of the study (whether symptomatic or not) should be reported by the Investigator or qualified designee as a protocol violation within 24 hours of the Investigator or qualified designee first becoming aware of the overdose. If an overdose results in an AE, the eCRF AE page should be completed, and source documents included. If the overdose results in an SAE, then SAE reporting should be followed using the specific eCRF pages with overdose information entered in the narrative section. All available clinical information relevant to overdose, including signs and symptoms, laboratory findings, and therapeutic measures or treatments administered, should be summarized and discussed. The overdose should also be captured on the appropriate FT-2102 exposure eCRF.

7.3 Classification of Adverse Events by Severity

The severity refers to the intensity of the AE. The Investigator must categorize the severity of each AE according to the NCI CTCAE version 4.03 (see Appendix 4). CTCAE guidelines can be referenced at the following website: http://ctep.cancer.gov/reporting/ctc.html.

For any term that is not specifically listed in the CTCAE scale, intensity will be assigned a grade of one through five using the following CTCAE guidelines:

Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

7.4 Classification of Adverse Events by Relationship to Study Drug Administration

The relationship of each AE to the study drug administration will be assessed by the Investigator; after careful consideration of all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication and dechallenge or rechallenge according to the following guidelines:

YES (possible, probably, or definitely related): there is a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environment, or toxic factors or other modes of therapy, administered to the patient
- The event follows a known pattern of response to study drug
- The event disappears or decreases on cessation or reduction in dose of the study drug. In some situations, an AE will not disappear or decrease in intensity upon discontinuation of the study drug despite other clear indications of relatedness

NO (unlikely, probably not related, or definitely not related): There is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment, or toxic factor or other modes of therapy administered to the patient
- The event does not follow a known pattern of response to study drug
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered

7.5 Adverse Events Qualifying for Reporting to Regulatory Authorities

The AEs that are serious and unexpected, and assessed as related to study drug, will be reported to the regulatory authorities by Forma Therapeutics, Inc. in accordance with local regulations. Serious, unexpected, and study drug-related events are to be reported to the regulatory authorities within 15 calendar days of initial notification to Forma Therapeutics, Inc. or its designee. If the AE is serious, unexpected, and related to study drug and is fatal or life threatening, the event will also be reported to the regulatory authorities within seven calendar days.

8 STUDY OR STUDY SITE TERMINATION AND PATIENT DISCONTINUATION

8.1 Study or Study Site Termination

If the Investigator, the Sponsor or Sponsor's Study Director or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, and Study Monitor. Criteria that may be considered when determining a potential termination of the study would be unacceptable toxicity and/or an unfavorable risk-benefit profile.

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Council on Harmonisation (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21, with appropriate notification of the FDA and all IRB's/EC's having approved the study protocol and ICF.

8.2 Treatment and Study Discontinuation

8.2.1 Treatment Discontinuation

Study treatment discontinuation occurs when a patient is no longer receiving any study drug (FT-2102, azacitidine, or cytarabine, as applicable). Treatment discontinuation is not necessarily accompanied by discontinuation from the study, as discussed in Section 8.2.2.

A patient should be discontinued from study treatment if, in the opinion of the Investigator, doing so is medically necessary, or if it is the wish of the patient. Reasons for discontinuation from study treatment may include any of the following:

- Unacceptable AE or failure to tolerate study therapy
- Delay in dosing of > 28 days, without approval of Sponsor
- Treatment failure (i.e., progression or relapse) (see Section 4.3, Table 3 for definition)
- Hematopoietic stem cell transplant (HSCT)
- Withdrawal of consent (no further study participation)
- Patient decision to discontinue study treatment
- Discretion of the Investigator
- Major protocol violation
- Pregnancy
- Lost to follow-up
- Death
- Termination of the study by Sponsor

All AEs leading to the discontinuation of study drug will be followed for 28 days after administration of last dose of study drug or until resolution or stabilization as documented by physical examination or appropriate laboratory results.

All patients who discontinue study treatment should undergo the End-of-Treatment assessments (see Section 6.1.23) and undergo Safety Follow-up (Section 6.1.24)/ enter Survival Follow-up (Section 6.1.26).

Patients who discontinue study treatment for reasons other than disease progression/relapse, including those who discontinue for HSCT, will continue to be followed for response duration until progression/relapse occurs (see Section 6.1.25).

Patients who discontinue treatment for HSCT should continue to be assessed for response as per the protocol-defined schedule.

8.2.2 Study Discontinuation

Patients may voluntarily withdraw from the study at any time for any reason without prejudice. Patients will be withdrawn from the study in the case of any of the following reasons:

- Death
- Lost to follow-up
- Completion of follow-up period
- Termination of the study by Sponsor
- Withdrawal of consent

9 DATA RECORDING, CRF PROCESSING, AND STATISTICAL ANALYSIS

9.1 Data Recording and CRF Processing

In place of recording patient data on paper CRFs, which will not be used in this study, site personnel are responsible for entering such data into the Electronic Data Capture (EDC) system. This system has been validated and is compliant with FDA, ICH, and European Union (EU) regulations and guidelines and with Department of Health and Human Services 21 CFR Part 11 rules for electronic records and electronic signatures. No data will be requested other than what is routinely written on paper CRFs.

An audit may be performed at any time during or after completion of the clinical study by Sponsor personnel or their designee. All study-related documentation must be made available to the designated auditor.

9.2 Statistical Analysis

9.2.1 General Considerations

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum (min), and maximum (max). If the measurements in the source (raw) data are integers, then the corresponding mean and median will be presented to 1 decimal place and the SD to 2 decimal places; if the measurements are obtained to 1 decimal place, then the mean and median will be presented to 2 decimal places and the SD to 3 decimal places; and so forth. Minimum and maximum will be displayed as reported in the source (raw) data. In addition, change from baseline values will be calculated at each timepoint and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified.

All analyses and summary outputs will be generated using SAS® version 9.3 (or higher).

All patient data, including those derived, will be presented in the patient data listings; listings will display for all patients, regardless of whether or not they received study drug. In general, the patient data listings will be sorted by treatment (dose levels), patient number and assessment visit and date (and time, if applicable). The summary tables will be presented descriptively overall and by treatment group.

For the purpose of all safety and efficacy analyses where applicable, baseline is defined as the last non-missing measurement prior to the start of study drug administration.

9.2.2 Sample Size

Sample size calculations are based on the primary objectives for each study cohort.

9.2.2.1 Phase 1

The primary objective for Phase 1 in this study is to evaluate DLT or identify MTD/MED and recommend a dose for Phase 2. Within the Phase 1 portion of the study, the Dose-Escalation Stage is based on a traditional 3+3 design to avoid selection of a dose going forward in development that causes a treatment-limiting toxicity in more than 17% of patients. At each dose level, 3 patients will be enrolled; if < 1/3 DLTs are identified, the dose will be escalated to the next dose level. If 1 DLT is identified, 3 additional patients will be added to the same dose level. If 1/6 DLT is identified, the study will be escalated to the next dose level. Otherwise, the MTD will be identified as the dose lower than the dose with > 1/6 DLTs.

The total number of patients who will be enrolled in the dose-escalation stage will depend on the number of DLTs observed within each dose cohort. It is anticipated that, at a minimum, doses of 150 mg and 300 mg FT-2102 QD will be tested as a single agent and in combination with azacitidine. If 6 patients are treated at each dose level, approximately 24 patients will be treated in the dose-escalation stage.

During the Phase 1 Dose-Expansion Stage, each of the non-LDAC cohorts would have 14 patients. With 20 patients treated (at least 6 from the dose-escalation stage, 14 from dose-expansion) at the determined MTD/MED, the probability of observing at least 1 incidence is > 87% for adverse events of true incidence rate of ≥17%. For the LDAC cohort, the selection of 6 patients is a minor variation of the traditional 3+3 design in order to identify the risk of LDAC for toxicities in more than 17% of patients.

9.2.2.2 Phase 2

The primary objective of Phase 2 is to evaluate the clinical activities of FT-2102 alone or in combination in patients with R/R AML or MDS and confirmed IDH1 mutation.

Cohort 1 (patients with R/R AML harboring IDH1-R132 mutations): A group sequential design is planned for this cohort with two interim analyses and a final test. One hundred seventy three (173) patients provide 90% power to test the null hypothesis that the true complete response rate (CR + CRh) is 15% or less versus the one-sided alternative hypothesis that the true complete response rate is greater than 15%, with a 2.5% significance level using a one-sided exact test for a binomial proportion, assuming the true response rate is 25%.

Two interim analyses are planned, at approximately 33% and 67% of the information. O'Brien-Fleming stopping boundaries will be used for both alpha and beta adjustments. At the first interim, if ≤ 6/58 responses are observed (or crude p-value ≥ 0.88), the trial may be stopped early for futility. The first interim analysis will be conducted on the Full Analysis Set (FAS) within Phase 2 Cohort 1. At the first interim analysis, the study is not intended to stop for efficacy. At the second interim analysis, if ≥ 28/115 responses are observed (or crude p-value is ≤ 0.0057), the trial may stop enrollment for efficacy and if there are 20 or fewer responses (or crude p-value is > 0.2718) the trial may be stopped for futility. The second interim analysis will be conducted

in the Efficacy Evaluable (EE) Set within Phase 2 Cohort 1. In the event of an early stop for efficacy, all enrolled patients would remain on treatment and their long-term efficacy data, such as EFS and OS, will continue to be observed.

If the study is not stopped early for efficacy or futility, at least 173 evaluable patients are planned to be enrolled. A one-sided exact test will be performed. If the one-sided p-value is ≤ 0.0245, the null hypothesis (the response rate is ≤ 15%) will be rejected, and the alternative hypothesis that the response rate is > 15% will be accepted. If exactly 173 patients are evaluable, this is equivalent to 36 or more responses observed.

To account for potential discordance between central and local testing of the IDH1-R132 mutation, approximately 190 patients are planned to be enrolled into this cohort.

Cohort 2 (patients with AML with persistent IDH1-R132 mutation + bone marrow demonstrating morphologic CR/CRi after prior therapy +/- HSCT): A Simon optimal two-stage design will be used. The null hypothesis that the true 4-month RFS rate is 80% will be tested against a one-sided alternative. In the first stage, 11 patients will be evaluated. If 9 or fewer of the first 11 patients are relapse-free at 4 months, the study will be stopped. Otherwise, 42 additional patients will be accrued, for a total of 53 patients. The null hypothesis will be rejected if 48 or more of these 53 patients are event-free at 4 months. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true 4-month RFS rate is 94%.

Cohorts 3-5 (patients with AML/MDS harboring IDH1-R132 mutations that are R/R to prior IDH1 inhibitor therapy; or naïve to hypomethylating and IDH1m inhibitor treatments; or R/R to prior hypomethylating therapy): A single-stage design with 20 patients will be used. If 4 or more complete responses are observed in these 20 patients, the lower bound of a one-sided 85% confidence interval based on an exact binomial distribution will be greater than 10%, thus supporting the hypothesis that the true complete response rate is greater than 10%.

Cohort 6 (patients with AML/MDS harboring IDH1-R132 mutations that are R/R to immediately prior SA IDH1 inhibitor therapy): A Simon's optimal two-stage design will be used. The null hypothesis that the true complete response rate is 15% will be tested against a one-sided alternative. In the first stage, 14 patients will be evaluated. If there are 2 or fewer complete responses in the first 14 patients, the study will be stopped. Otherwise, 30 additional patients will be accrued for a total of 44 patients. The null hypothesis will be rejected if 11 or more complete responses are observed in these 44 patients. This design yields a 1-sided type I error rate of 0.05 and power of 80% when the true complete response rate is 32%. The probability that the trial will be stopped at the end of the first stage if the true complete response rate is 10% is 0.65.

Cohort 7 (treatment naïve AML patients for whom standard treatments are contraindicated): A Simon's optimal two-stage design will be used. The null hypothesis that the true complete response rate is 25% will be tested against a one-sided alternative. In the first stage, 17 patients will be evaluated. If there are 5 or fewer complete responses in the first 17 patients, the study will be stopped. Otherwise, 37 additional patients will be accrued for a total of 54 patients. The null hypothesis will be rejected if 20 or more complete responses are observed in these 54 patients. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true complete response rate is 45%.

Cohort 8 (treatment naïve AML patients who are candidates for azacitidine first line treatment): A Simon's optimal two-stage design will be used. The null hypothesis that the true complete response rate is 25% will be tested against a one-sided alternative. In the first stage, 7 patients will be evaluated. If there are 2 or fewer complete responses in the first 7 patients, the study will be stopped. Otherwise, 21 additional patients will be accrued for a total of 28 patients. The null hypothesis will be rejected if 12 or more complete responses are observed in these 28 patients. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true complete response rate is 55%.

9.2.3 Analysis Sets

DLT-Evaluable Set will include all patients in dose escalation who have received at least one dose of FT-2102 and completed at least 75% of doses in the first cycle during the DLT evaluation period, or have discontinued due to adverse events meeting the DLT evaluation criteria. This set will be used for DLT analyses only, unless otherwise specified.

Safety Analysis Set will include all patients who have received at least one dose of study drug (FT-2102, azacitidine, or cytarabine). All safety analyses will be based on the Safety Set unless otherwise specified. Patients will be analyzed under the first dose level received by the patient.

Full Analysis Set (FAS) will include all patients who were enrolled in the study and received at least one dose of FT-2102. This analysis set will be used for efficacy analyses. Patients will be analyzed under the assigned dose.

Efficacy Evaluable (EE) Set will include all patients in Phase 2 Cohort 1 with confirmed IDH1-R132 (by central lab) who have received the first dose of FT-2102 at least 6 months prior to the analysis cutoff date or who have died, progressed, or discontinued study participation. This analysis set is the primary set for the Phase 2, Cohort 1 efficacy evaluation. Patients will be analyzed by assigned dose.

Per Protocol (PP) Analysis Set is a subset of patients in the EE set, excluding patients who have protocol violations that could impact the evaluation of the efficacy of FT-2102. Some violations that would result in exclusion from the PP Analysis Set are: not meeting all inclusion/ exclusion criteria for a particular cohort, having received chemotherapy not per protocol, received starting dose of FT-2102 other than 150 mg BID, not having at least one post-baseline response assessment. The full list of protocol violations will be reviewed on a de-identified basis by the medical, data management, and statistical leads prior to locking the database, and membership in the PP Analysis Set will be documented and determined based on that review.

PK Analysis Set consists of patients for whom it is possible to calculate at least one primary PK parameter (e.g. C_{max}, AUC_{last} and AUC_{inf}) and who do not have any major protocol deviations thought to influence the absorption, distribution, metabolism and excretion of the FT-2102.

PD Analysis Set consists of all patients who have received at least one dose of FT-2102 and have completed at least one PD assessment. The PD Analysis Set will be used for PK/PD-related analyses unless otherwise specified.

9.2.4 Analysis of Clinical Data

9.2.4.1 Demographic and Tumor Characteristics

Baseline demographic and tumor characteristics will be summarized using descriptive statistics (n, mean, median, minimum, maximum, standard deviation [SD], standard error [SE] for continuous variables; n, percent for categorical variables) for each cohort using the cohort to which they were initially assigned, and all patients will be accounted for.

9.2.4.2 Safety Analysis

For DLT-evaluable patients, the summary of DLTs will be provided by dose/dosing schedule for patients in the Phase 1 dose-escalation stage. All other safety analyses will be based on the Safety Set.

For each stage, the safety and tolerability of FT-2102 will be assessed, as evaluated by adverse events, concomitant medication usage, changes from baseline in physical examination, vital signs, clinical laboratory evaluations, and ECG. Safety data will be listed by patient and summarized descriptively.

A treatment-emergent adverse event (TEAE) is defined as an adverse event with onset on or after the start of study drug, or any worsening of a pre-existing medical condition/adverse event with onset on or after the start of study drug and until 28 days after the last dose. For each stage, all adverse events will be coded using MedDRA version 19.1 or higher and summarized by SOC and PT, for each treatment group. Multiple occurrences of an AE are counted only once per patient per SOC and PT for summary tables. Causality of TEAEs (not related, related) and severity (NCI CTCAE version 4.03 or higher) will be summarized by treatment for each stage.

Relationship will be presented by study drug when applicable. All adverse events and serious adverse events (including those with onset or worsening before the start of study drug) will be listed.

Safety laboratory, vital sign, ECG and physical examinations will be summarized by visit. The change from baseline will be presented along with the by-visit summaries. Shifts in laboratory grades, as well as QTcF shifts, will be tabulated. Assessment of changes in liver function tests will be conducted. Abnormal safety assessments will be flagged and separately presented. All safety data will be listed.

Assessment of differentiation syndrome will be conducted as per Montesinos et al. 2009, searching for candidate cases of differentiation syndrome based on AE reports of dyspnea, pulmonary infiltrates, edema, weight gain, pleural effusion, renal failure, hypotension, pericardial effusion, and unexplained fever. Specific methods of identifying candidate cases will be fully described in the Statistical Analysis Plan (SAP).

9.2.4.3 Antileukemic and Antimyelodysplastic Activity

All analysis in the section will be based on patients in the EE Set as the primary analysis, with additional analyses on the FAS, and in some cases the PP Set as supportive.

Primary Efficacy Endpoints and Hypotheses

CR/ CRh Rate

The primary efficacy endpoint for all Phase 2 cohorts, with the exception of Cohort 2, is the CR/CRh rate (defined as bone marrow blasts < 5% with complete (CR) or partial (CRh) hematologic recovery; see Appendix 7 and Appendix 8 for complete definition). The CR/CRh rate will be calculated and presented together with the Clopper-Pearson 95% confidence interval for each cohort.

For Phase 2, Cohort 1, to test the hypothesis that the complete response rate is greater than 15%, a 1-sided exact test for a binomial proportion will be performed. If the exact 1-sided p-value is less than 0.023, the alternative hypothesis will be accepted. This is equivalent to at least 36 CR/CRh responses of 173 EE patients.

For Phase 2, Cohorts 3, 4, and 5 test the hypothesis that the 85% confidence interval for the complete response rate does not include 10%. If there are 5 or more complete responses of the 20 patients in these cohorts, the 85% confidence interval will be greater than 10%, and the alternative hypothesis that the response rate is greater than 10% will be accepted.

Phase 2 Cohorts 6, 7, and 8 are Simon 2-Stage designs and the primary efficacy endpoint will be evaluated via the number of CR/CRh responses stipulated in the design criteria described in Section 9.2.2.

4-Month RFS

The primary endpoint for Phase 2 Cohort 2 is the 4-Month RFS. This will be evaluated by a Simon 2-Stage design described in Section 9.2.2, testing the null hypothesis that the 4-month RFS is < 80%. It is defined as the proportion of patients who have not relapsed or died on or before their 4-month response evaluation. If a patient does not receive a disease response assessment at their 4-month visit but has a subsequent disease response assessment on or after study day 120 that shows non-progression/ non-relapse, they will be evaluated as having achieved 4-month RFS.

Secondary Efficacy Endpoints

CRi, MLFS, Marrow CR, and PR definitions will be derived from the IWG response criteria (see Section 4.3, Appendix 7 and Appendix 8) for AML (2003) and MDS (2006) based on investigator's assessment.

Transfusion independence, defined as the proportion of patients who have received a packed red blood cell or platelet transfusion in the eight weeks prior to first dose of FT-2102 who have a 28-day period during any point on study with no transfusion required. Additionally, the number of patients who are transfusion independent for at least 56 consecutive days will also be summarized. Percent of transfusion independence will be calculated based on the number of patients who were transfusion dependent prior to first dose of FT-2102.

For each cohort, the number and percentage of the best overall response will be presented by response category and by treatment group. Other binomial endpoints including overall response rate (CR + CRh + CRi + MLFS + PR) and rate of responses in the individual response category, will also be analyzed. Number and percentage of patients within each response category will be presented by dose/dosing schedule and visit. Clopper-Pearson 95% confidence intervals will be provided along with the responses.

Overall survival for all cohorts at landmark timepoints will be analyzed.

Time to event data will be analyzed using Kaplan-Meier (KM) methods for each cohort. The median time will be tabulated along with the 95% Brookmeyer Crowley confidence intervals. The estimated probability of survival over time will be plotted as KM curves for each cohort (or by disease type and by treatment).

Detailed considerations for all time to event variables are provided in the SAP.

Additional efficacy analyses will be specified in the SAP.

9.2.5 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed in patients in the PK Analysis Set.

Concentration-time profiles will be constructed from the plasma samples obtained. Estimates of the AUC and slope of the terminal decay phase will be used to calculate values of the following PK parameters: $t_{1/2}$, CL/F, T_{max}, and Vd/F. The plasma profiles will also be fitted by nonlinear regression analysis whenever possible. An analysis of variance or corresponding nonparametric statistical tests will be applied:

- To compare mean values of PK variables and parameters determined at different doses and
- To identify the existence of trends in C_{max} and/or metabolite concentrations within patients that may be suggestive of drug accumulation or alterations in PK behavior.

9.2.6 Pharmacodynamic Analysis

Pharmacodynamic analysis will be performed in patients in the PK Analysis Set.

All PD data will be presented in tabular and/or graphical format and summarized descriptively. Absolute change from baseline and/or percentage change from baseline will be summarized by dose level. Patients in the dose expansion portion of this study will be considered a separate cohort for the purposes of these presentations.

9.2.7 Genotypic Analysis

All genotypic data will be presented in tabular and/or graphical format and summarized descriptively. Cancer-associated mutations and/or genetic alterations will be correlated with responding and nonresponding patients. Patients in the dose expansion portion of this study will be considered a separate cohort for the purposes of these presentations.

9.2.8 Quality of Life Analysis

Quality of life, as assessed by the EQ-5D-5L, will be analyzed for patients in the EE and FAS. EQ-5D-5L data will be summarized from the screening visit through cycle 4 for the FAS and EE Analysis sets (Phase 2). The number and percentage of patients reporting each score per dimension will be summarized, as well as the number reporting some problems on that dimension (score > 1). Also the change from baseline in the number reporting some problems in each dimension will be reported (raw and percent change). Additional analyses and techniques for handling missing data will be described in the SAP.

9.2.9 Interim Analysis

Interim analyses will be performed for the Phase 2 Cohort 1 and in other applicable Phase 2 cohorts that use two-stage designs, at defined timepoints. These are described in Section 9.2.2.2. As a result of these analyses, enrollment in a given cohort may be stopped early either for efficacy or futility.

10 ADMINISTRATIVE ASPECTS

10.1 Institutional Review Board/Ethics Committee

This protocol and the proposed informed consent form must be reviewed and approved by the appropriate IRB/EC, prior to the start of the study. The proposed informed consent form must also be agreed to by Forma Therapeutics, Inc. or their designee. A copy of the IRB/EC approval letter of the protocol, any amendments, and the ICF must be supplied to Forma Therapeutics, Inc. or their designee prior to starting the study.

During the course of the study, the Investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB/EC must be provided to Forma Therapeutics, Inc. or their designee.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved by Forma Therapeutics, Inc. (and may require other review and/or approval) and must be approved in writing by the IRB/EC prior to implementation. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately provided that Forma Therapeutics, Inc. is immediately notified and an amendment is subsequently provided by Forma Therapeutics, Inc. and approved by the IRB/EC.

It is the Investigator's obligation to maintain an IRB/EC correspondence file and to make this available for review by Forma Therapeutics, Inc. representatives or their designee as part of the study monitoring process.

10.2 Informed Consent and Authorization for Use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of PHI must be obtained from each patient (or the patient's legal representative) prior to performing any study-specific Screening Period evaluations. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations. The proposed informed consent form must be in compliance with regulatory regulations and must have been reviewed and approved by Forma Therapeutics, Inc. and the Investigator’s IRB/EC prior to initiation of the study. The proposed informed consent form should contain the 20 elements of informed consent described in ICH E6 4.8, including a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of patient study records, a statement regarding voluntary compensation and availability of treatment in the case of injury, an explanation of whom to contact about the research, the patient’s rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits.

These requirements are in accordance with the Code of Federal Regulations as detailed in the 21 CFR 50.25 and the Declaration of Helsinki. It should also indicate by signature that the patient, or where appropriate, legal guardian/representative, permits access to relevant medical records

by Forma Therapeutics, Inc. staff, Forma's duly appointed representatives, and by representatives of the United States (US) Food and Drug Administration (FDA) or other applicable regulatory agency. Additionally, Investigators in states with specific regulations regarding patients' rights have a responsibility to follow and document their fulfillment of those regulations.

The Investigator will be responsible for obtaining written informed consent from potential patients or the patient's legally authorized representative prior to any study specific screening and entry into the study, and also additional consent for future research provisions (see ICF). A copy of the signed document will be provided to the patient, and a copy will be maintained with the patient's eCRFs, or in the study documentation notebook. The original will be retained by the Investigator along with the eCRFs. The source documents for each individual shall document that informed consent was obtained prior to participation in the study.

10.3 Delegation of Investigator Responsibilities

The Investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and study-related duties.

10.4 Study Documentation

10.4.1 Investigator Information

Investigator information is included in the Study Procedures Manual, which is updated regularly.

10.4.2 Laboratory Accreditation

Any laboratory facility to be used for analysis of routine clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Licensure/accreditations and reference values and/or normal ranges for the test results must be provided to Forma Therapeutics, Inc.

Forma Therapeutics, Inc. must be notified immediately in writing of any changes occurring in reference values during the course of the study.

10.4.3 Study Files

Documentation concerning Investigator data and IRB/EC data is required prior to shipment of study drug to the study site. Copies of these documents as well as supplemental information, such as the IB and Responsibilities and Obligations of Investigators and Sponsors, will be kept on-site in an Investigator study file binder. This file also will contain drug accountability (receipt/dispensing) records, Sponsor/Investigator correspondence, IRB/EC correspondence, changes to the protocol, information regarding monitoring activities, patient exclusion records,

biological sample records, and eCRFs.

10.4.4 Source Documentation

The Investigator must make study data accessible to the Sponsor, to other authorized representatives of the Sponsor, and to the appropriate regulatory authority inspectors. The eCRF for each patient will be checked against source documents at the study site by the Study Monitor.

10.4.5 Retention of Study Documents

According to ICH E6 4.9, all eCRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

10.5 Confidentiality

10.5.1 Data

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/EC, the patient, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

10.5.2 Patient Anonymity

The anonymity of participating patients must be maintained. Patients will be identified by an assigned patient number on eCRFs and other documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the patient (eg, the signed ICF) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

10.6 Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of patients or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of patients treated, or the patient selection criteria. Such changes must be prepared as a protocol amendment by the Study Monitor only upon joint approval of the Sponsor, Investigator, and the Study Monitor. A protocol amendment

must receive IRB/EC approval prior to implementation. In parallel with the IRB/EC approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes to the ICF, the revised ICF prepared by the Investigator must be reviewed by the Sponsor and the Study Monitor and approved by the IRB/EC.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed crucial for the safety and well-being of that patient may be instituted for that patient only.

The Investigator or other attending physician also will contact the Sponsor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB/EC; however, the IRB/EC and Sponsor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the patient's eCRF the reasons for the protocol deviation and the ensuing events.

10.7 Monitoring Functions and Responsibility

Throughout the course of the study, the Forma Therapeutics, Inc. representatives, or monitors designated by Forma Therapeutics, Inc., may make frequent contacts with the Investigator. This may include telephone and/or on-site visits at appropriate and necessary intervals.

The Investigator or appointed delegate will be available to the Forma Therapeutics, Inc. representative(s) during on-site visits and will provide necessary study documents for inspection and will respond to all inquiries that may arise as part of this review. On completion of the study, the Forma Therapeutics, Inc. monitor(s) may arrange for a final review of the study files after which the files should be secured for the appropriate time period as specified in Section 10.4.5 (or Section 10.9). The Investigator will also permit inspection of the study files by authorized representatives of the FDA or other applicable regulatory agency.
The progress of the study will be monitored by using the following methods:

- Periodic on-site visits
- Frequent telephone and written communications between the Investigator, Sponsor, and the Study Monitors
- Review of eCRFs and clinical records

10.8 Drug Accountability

The investigational drug is to be prescribed only by the Principal Investigator or physician subinvestigators named on Form FDA 1572 and submitted to the IND for FT-2102. Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol.

The Investigator must maintain accurate records that account for the receipt of the investigational drug supplies using the Sponsor’s Investigational Materials Shipping Order and for the

disposition of the drug using dispensing records, which identify the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned. This record is in addition to any drug accountability information recorded on the case report forms. At the termination of the study or at the request of the Sponsor, the Investigator will destroy or return unused study medication and all partially dispensed or empty containers.

10.9 Record Retention

Records of drug receipt and disposition, eCRF, and reports of this investigation must be maintained by the Investigators for a period of at least two years following the date on which the investigational drug is approved by the FDA or other applicable regulatory agency for marketing, for the purposes that were the patient of the clinical investigations. If no application is to be filed, records must be retained until two years following the date that the study is discontinued and the FDA or other applicable regulatory agency is notified. If the application is not approved by the FDA or other applicable regulatory agency for such indication, records must be retained for two years after notification by Forma Therapeutics, Inc. of the FDA or other applicable regulatory agency decision. Forma Therapeutics, Inc. should be notified in writing at least 30 days prior to the disposal of any study records related to this protocol.

10.10 Financial Disclosure

The Investigator and subinvestigators, as noted on the Form FDA 1572, shall provide Forma Therapeutics, Inc. with sufficient accurate financial disclosure information to allow Forma Therapeutics, Inc. to submit complete and accurate certification or disclosure statements as required under 21 CFR 312.54.

The Investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

10.11 Patient Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of patients during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of regulatory authorities to inspect, for purposes of verification, the hospital or clinic records of all patients in this study.

10.12 Disclosure of Data

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. The conditions regulating dissemination of the information derived from this clinical trial are described in the Clinical Trial Agreement.

10.13 Publication Agreement

The conditions regulating publications derived from this clinical trial are described in the Clinical Trial Agreement.

10.14 General Information

The Investigator should refer to the associated IB, the Study Procedures Manual, information provided during the study initiation visit, information provided by the Study Monitor, and the appendices of this clinical study protocol for further information regarding this investigational new product or details of the procedures to be followed during the course of this study.

11 REFERENCES

Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. *Clin Lymphoma Myeloma Leuk.* 2016;16(8):460-5.

Borodovsky A, Salmasi V, Turcan S, et al. 5-azacytidine reduces methylation, promotes differentiation and induces tumor regression in a patient-derived IDH1 mutant glioma xenograft. *Oncotarget*. 2013; 1-11.

Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: Mechanisms, models, and clinical opportunities. *Cancer Discov*. 2013; 3:730-741.

Cheson BD, Bennett JM, Kopecky KJ, *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards of Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003; 21:4642-4649.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108(2): 419-25.

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

de Botton S, Pollyea DA, Stein EM, et al. Clinical safety and activity of AG-120, a first-in-class potent inhibitor of the IDH1 mutant protein, in a Phase 1 study of patients with advanced, IDH1-mutant hematological malignancies. 20th Congress of the European Hematology Association 2015, Abstract P563.

DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018 Jun 21;378(25):2386-2398.

Fan, B, Chen Y, Wang F, et al. Pharmacokinetic/pharmacodynamics evaluation of AG-120, a potent inhibitor of the IDH1 mutant protein, in a Phase 1 study of IDH-1 mutant advanced hematologic malignancies. 20th Congress of the European Hematology Association 2015, Abstract P572.

Fathi AT, DiNardo CD, Kline I, et al. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2. Analysis of a Phase 1/2 study. *JAMA Oncol*. 2018;4(8):1106-1110.

Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med.* 1992 Aug 15;117(4):292-6.

Gross S, Cairns RA, Minden MD, et al. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med*. 2010; 207(2):339-44.

Laufer CB, Roberts O. Differentiation syndrome in acute myeloid leukemia after treatment with azacitidine. *Eur J Haematol*. 2015; 95(5):484-5.

Lee SH, Erber WN, Porwit A, Tomonaga M, Peterson LC; International Council for Standardization In Hematology. ICSH guidelines for the standardization of bone marrow specimens and reports. Int J Lab Hematol. 2008 Oct;30(5):349-64. doi: 10.1111/j.1751-553X.2008.01100.x.

Losman JA, Looper RE, Koivunen P, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. *Science*. 2013; 339(6127):1621-1625.

Mardis, E, Ding L, Dooling D, et.al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009; 361:1058-1066.

Montesinos P, Bergua JM, Vellenga E, Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood*. 2009 Jan 22;113(4):775-83.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am. J. Clin Oncol*. 1982; 5:649-655.

Rohle D, Popovici-Muller J, Palaskas N, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science*. 2013; 340 (6132):626-630.

Saha SK, Parachoniak CA, Ghanta KS, et al. Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. *Nature.* 2014; 513:110-114.

Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017 Aug 10;130(6):722-731. doi: 10.1182/blood-2017-04-779405.

UNC Lineberger Comprehensive Cancer Center. Simon's Two Stage Design. Available at http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx.

Yen K, Lemieux R, Popovici-Muller J, et al. IDH1 mutant inhibitor induces cellular differentiation and offers a combination benefit with Ara-C in a primary human IDH1 mutant AML xenograft model. *Blood*. 2013, 122:3946.

Appendix 1 Schedule of Events (Ongoing Patients)

Study Procedures	**Pre-screening (Optional)**	**Screening (D -14 to D1)**	**Cycle 1**									**Cycle 2**						**Cycle 3**		**Cycle 4**	**Cycle 5 and beyond**	**End of Tx[b]**	**28-day Follow-up[c]**	**Survival Follow-up**
Days			**D1**	**D2**	**D5 ± 1D**	**D8 ± 1D**	**D12 ± 2D**	**D15 ± 2D**	**D19 ± 2D**	**D22 ± 2D**	**D26 ± 2D**	**D1 ± 2D**	**D2 ± 2D**	**D4 ± 2D**	**D8 ± 2D**	**D15 ± 2D**	**D22 ± 2D**	**D1 ± 3D**	**D15 ± 2D**	**D1 ± 3D**	**D1 ± 3D Every other cycle[a]**	**± 7D**	**+ 7D**	**q 3 mo**
Signed Informed Consent[d]		X[d]																						
Complete Medical History[e]		X																						
Concomitant Medications		X	X	X[f]		X		X		X		X				X		X		X	X	X	X	
Height and Weight[g]		X	X									X						X		X	X	X		
Vital Signs[h]		X	X			X		X		X		X				X		X		X	X	X		
ECOG PS		X	X									X						X		X	X	X		
Physical Examination		X	X			X[i]		X[i]		X[i]		X[i]				X[i]		X[i]		X[i]	X[i]	X		
Serum or Urine Pregnancy Test[j]		X	X									X						X		X	X	X		
12-lead ECG[k]		X	X[k]			X[k]		X[k]		X[k]		X[k]				X[k]		X		X	X[l]	X[l]		
Holter Monitoring (Phase 2 only)[m]			X	X								X	X											
Clinical Serum Chemistries[n,o]		X	X		X[p]	X	X[p]	X	X[p]	X	X[p]	X			X[p]	X	X[p]	X	X[p]	X	X	X		
CBC with Differential and Platelet Count[o,q]		X	X		X[p]	X	X[p]	X	X[p]	X	X[p]	X			X[p]	X	X[p]	X	X[p]	X	X	X		
Coagulation Parameters[r]		X										X												
Bone Marrow Aspirate[s]		X										X						X		X	X	X		
Urinalysis[o,t]		X	X									X						X		X		X		

Study Procedures	Pre-screening (Optional)	Screening (D -14 to D1)	Cycle 1									Cycle 2						Cycle 3		Cycle 4	Cycle 5 and beyond	End of Tx[b]	28-day Follow-up[c]	Survival Follow-up
Days			**D1**	**D2**	**D5 ± 1D**	**D8 ± 1D**	**D12 ± 2D**	**D15 ± 2D**	**D19 ± 2D**	**D22 ± 2D**	**D26 ± 2D**	**D1 ± 2D**	**D2 ± 2D**	**D4 ± 2D**	**D8 ± 2D**	**D15 ± 2D**	**D22 ± 2D**	**D1 ± 3D**	**D15 ± 2D**	**D1 ± 3D**	**D1 ± 3D Every other cycle[a]**	**± 7D**	**+ 7D**	**q 3 mo**
AE Monitoring			Continuous																				X	
PK (Peripheral Blood)[u]			X	X		X		X		X		X[v]	X	X		X		X		X				
PD (Peripheral Blood)[w]	X[x]	X	X	X		X		X		X		X	X	X		X		X		X				
EQ-5D-5L (Phase 2 only)		X[y]										X						X		X				
Study Drug Diary[z]			X									X						X		X	X			
Study Drug Admin[aa,bb,cc]			Drug will be given in accordance with the dosing schedules for FT-2102, azacitidine and LDAC																					
Survival[dd]																							X	X

Admin = administration; AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; Ca = calcium; CBC = complete blood count; Cl = chloride; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FSH = follicle-stimulating hormone; K = potassium; LDAC = low dose cytarabine; LDH = lactate dehydrogenase; LH = luteinizing hormone; MDS = myelodysplastic syndrome; Mg = magnesium; Na = sodium; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; PTT = partial thromboplastin time; Tx = treatment.

NOTE: All assessments will be conducted predose unless specified otherwise.

[a] Beginning with Cycle 5, scheduled assessments will be performed every 2 cycles.
[b] End of Treatment visit to be conducted within 7 days of the decision to discontinue treatment. End of Treatment assessments need not be repeated if they were completed within the previous 2 weeks (4 weeks for bone marrow assessments).
[c] 28-day Follow-up visit to be conducted within 28 days (+ 7 days) of last dose for adverse event follow-up and to capture initiation of new therapies (con-medications).
[d] Informed consent must be completed prior to the initiation of any study-specific procedures or assessments. The informed consent process may be completed prior to the Screening Period (i.e., before Day -14) (see Section 6.1.2).
[e] Includes complete surgical and cardiac history and complete leukemia or MDS medical history. Complete leukemia or MDS medical history will include applicable treatment history as well as cytogenetic risk categorization at diagnosis by NCCN or ELN guidelines.
[f] Only required in patients enrolled in Phase 1 and patients in Phase 2 participating in Holter monitoring.
[g] Height at Screening only.
[h] Includes temperature, blood pressure, pulse rate, and respiratory rate. Prior to dosing on Days 1, 8, 15, and 22 (Cycle 1); Cycle 2 predose on Days 1 and 15 and Cycle 3 and beyond predose on Day 1.
[i] Symptom-directed physical examination due to specific findings or abnormalities.

[j] To be performed on all female patients of childbearing potential and within 72 hr of dosing (Day 1 only of every cycle). At Screening, women aged 55 and under, are not surgically sterile, and who are amenorrheic must have LH, FSH, and estradiol measurements within the postmenopausal range for the institution, to be considered of nonchildbearing potential. A serum pregnancy test is required at Screening; serum or urine pregnancy tests are allowed for post-Screening visits.

[k] Phase 1: Electrocardiograms will be performed in triplicate (within a 10-minute period) predose and at 2 (± 15 minutes), 4 (± 15 minutes), and 8 hr postdose (± 30 minutes) on Cycle 1 Day 1 and Cycle 2 Day 1, and predose at all study visits where indicated. Phase 2: Electrocardiograms will be performed in triplicate (within a 10-minute period) predose on Cycle 1 Day 1 and Cycle 2 Day 1, and at all study visits where indicated. All electrocardiograms will be performed in a supine position.

[l] Electrocardiograms performed as clinically indicated for Cycle 5 and beyond.

[m] 24-hour 12-lead continuous Holters will be collected on C1D1 and C2D1 for patients at all centers in the US and select centers ex-US. The Holters should run from approximately 1 hour before dosing until 24 hours (the next day). Patients should remain supine for 10-15 minutes before and 5 minutes after ECG collection. See manual for further guidance on Holter monitoring.

[n] Clinical serum chemistries to include Na, K, Cl, bicarbonate, Mg, Ca, BUN, creatinine, AST, ALT, ALP, albumin, total bilirubin, direct bilirubin (collected only if total bilirubin is abnormal), LDH, glucose, amylase, lipase, uric acid, and thyroid function test (TFT) panel, which includes thyroid-stimulating hormone, free T3, and T4. In addition to the other chemistry panels, TFT panel is to be completed at Screening, C1D1, C2D1, and C3D1, then as clinically indicated.

[o] May be performed from 48 hr (Cycle 2) or 72 hr (Cycle 3 and 4) prior to Day 1 of a cycle (see Section 6.1).

[p] Clinical serum chemistries and CBC with differential and platelet count only at these study visits. May be performed through local laboratory testing.

[q] Includes hemoglobin, hematocrit, platelets, and white blood cell count with differential.

[r] Includes PT and PTT.

[s] Bone marrow aspirate for response assessment as described in Section 4.3. Refer to the laboratory manual for details of sample collection timing.

- Local IDH confirmation may have occurred > 28 days prior.
- C3D1 to be done on any patient who did not undergo a C2D1 bone marrow aspirate or biopsy.
- Patients who discontinue study treatment for reasons other than treatment failure and have not withdrawn consent from overall study participation, should continue to be followed for disease response assessments until the time of disease progression/relapse or the initiation of a new treatment regimen. Patients who have stopped FT-2102 treatment for HSCT should continue to be followed until disease progression/ relapse. This information should be documented on the appropriate eCRF page

[t] Urinalysis parameters include specific gravity, pH, total protein, protein, glucose, ketones, and blood. Microscopic examinations are to be performed as clinically indicated. For Cycle 3 & beyond and End of Study visit, urinalysis to be performed if clinically indicated.

[u] Blood samples will be collected for measurement of plasma concentrations of FT-2102 (single agent) or FT-2102 + azacitidine (combination agent). Blood will be collected relative to FT-2102 administration as described in Section 6.4 and Table 4.

[v] A 72-hour wash-out post C2D1 dosing will be requested from all patients participating in the dose-expansion stage. After the C2D1 FT-2102 AM dose, patients will be asked to refrain from taking FT-2102 until the AM of C2D4. PK samples will be collected on C2D2 and C2D4*.

[w] Blood samples will be collected for PD biomarker analysis for single agent FT-2102 and FT-2102/azacitidine combination. Blood will be collected relative to FT-2102 administration as described in Section 6.5 and Table 5.

[x] Optional pre-screening blood sample for 2-HG level detection and IDH1 mutation testing (in 2-HG abnormal).

[y] EQ-5D-5L survey can be completed anytime during screening prior to C1D1 dose.

[z] Study drug diary should be distributed by the site to the subject at each clinic visit and collected at the next clinic visit.

[aa] Single agent (FT-2102): FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days. On C1D1 only a single dose of FT-2102 is taken.

[bb] Combination agent (FT-2102 + azacitidine): azacitidine will be administered via subcutaneous injection or intravenous infusion in combination with oral FT-2102 for 7 days, and then azacitidine will be stopped for 21 days; a 48-hr dose interruption of the azacitidine for weekends or holidays is allowed. On C1D1 and C2D1, azacitidine is to be administered immediately prior to FT-2102 (to enable consistent PK assessments). On all other days and cycles when FT-2102 and azacitidine are co-administered, it is recommended to dose FT-2102 prior to azacitidine.

[cc] Combination FT-2102 + cytarabine: cytarabine will be administered at a dose of 20 mg BID subcutaneously (SC) for 10 days every 28-day cycle

[dd] After a patient discontinues study treatment and has completed their last study treatment visit, the study site may contact the patient approximately every 3 months to collect survival data and data pertaining to any other alternative anti-neoplastic therapy the patients begins for up to 12 months from the time of their 1st dose of study drug for the Phase 1 part of the study and up to 36 months for the Phase 2 part of the study. Patients who discontinue for reasons other than disease progression or who withdraw consent will continue to be followed for response until progression occurs.

* Not required in Phase 2.

Appendix 2 Schedule of Events (Patients Enrolled After Protocol Version 7/ Amendment 6)

Study Procedures	Screening (D -14 to D1)	Cycle 1 and beyond	End of Tx[b]	28-day Follow-up[c]	Survival Follow-up
Days		D1 ± 3D Every other cycle[a]	± 7D	+ 7D	q 3 mo
Signed Informed Consent[d]	X[d]				
Complete Medical History[e]	X				
Concomitant Medications	X	X	X	X	
Height and Weight[f]	X	X	X		
Vital Signs[g]	X	X	X		
ECOG PS	X	X	X		
Physical Examination	X	X[h]	X		
Serum or Urine Pregnancy Test[i]	X	X	X		
12-lead ECG	X	As clinically indicated	X[j]		
Clinical Serum Chemistries[k,l]	X	X	X		
CBC with Differential and Platelet Count[m]	X	X	X		
Coagulation Parameters[n]	X	As clinically indicated			
Bone Marrow Aspirate[o]	X	X	X		
AE Monitoring	Continuous			X	
Study Drug Diary[p]		X			
Study Drug Admin[q,r]		Drug will be given in accordance with the dosing schedules for FT-2102 and azacitidine			
Survival[s]					X

Admin = administration; AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; Ca = calcium; CBC = complete blood count; Cl = chloride; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FSH = follicle-stimulating hormone; K = potassium; LDH = lactate dehydrogenase; LH = luteinizing hormone; Mg = magnesium; Na = sodium; PT = prothrombin time; PTT = partial thromboplastin time; Tx = treatment.

NOTE: All assessments will be conducted predose unless specified otherwise.

[a] Scheduled assessments will be performed every 2 cycles.

[b] End of Treatment visit to be conducted within 7 days of the decision to discontinue treatment. End of Treatment assessments need not be repeated if they were completed within the previous 2 weeks (4 weeks for bone marrow assessments).

[c] 28-day Follow-up visit to be conducted within 28 days (+ 7 days) of last dose for adverse event follow-up and to capture initiation of new therapies (con-medications).

[d] Informed consent must be completed prior to the initiation of any study-specific procedures or assessments. The informed consent process may be completed prior to the Screening Period (i.e., before Day -14) (see Section 6.1.2).

[e] Includes complete surgical and cardiac history and complete leukemia medical history. Complete leukemia medical history will include applicable treatment history as well as cytogenetic risk categorization at diagnosis by NCCN or ELN guidelines.

[f] Height at Screening only.

[g] Includes predose temperature, blood pressure, pulse rate, and respiratory rate.

[h] Symptom-directed physical examination due to specific findings or abnormalities.

[i] To be performed on all female patients of childbearing potential and within 72 hr of dosing (Day 1 only of every cycle). At Screening, women aged 55 and under, are not surgically sterile, and who are amenorrheic must have LH, FSH, and estradiol measurements within the postmenopausal range for the institution, to be considered of nonchildbearing potential. A serum pregnancy test is required at Screening; serum or urine pregnancy tests are allowed for post-Screening visits.

[j] Electrocardiograms performed as clinically indicated.

[k] Clinical serum chemistries to include Na, K, Cl, bicarbonate, Mg, Ca, BUN, creatinine, AST, ALT, ALP, albumin, total bilirubin, direct bilirubin (collected only if total bilirubin is abnormal) conducted as indicated.

[l] Clinical serum chemistries also include LDH, glucose, amylase, lipase, uric acid, and thyroid function test (TFT) panel (including thyroid-stimulating hormone, free T3, and T4) conducted at Screening then as clinically indicated.

[m] Includes hemoglobin, hematocrit, platelets, and white blood cell count with differential.

[n] Includes PT and PTT.

[o] Bone marrow aspirate for response assessment to be done at Screening (if not taken at End of Treatment prior to roll-over) and then every 6 cycles unless there is suspicion of relapse/progression (see Section 4.3). Refer to the laboratory manual for details of sample collection timing.

- Local IDH confirmation may have occurred > 28 days prior.
- Patients who discontinue study treatment for reasons other than treatment failure and have not withdrawn consent from overall study participation, should continue to be followed for disease response assessments until the time of disease progression/relapse or the initiation of a new treatment regimen. Patients who have stopped FT-2102 treatment for HSCT should continue to be followed until disease progression/ relapse. This information should be documented on the appropriate eCRF page

[p] Study drug diary should be distributed by the site to the subject at each clinic visit and collected at the next clinic visit.

[q] Single agent (FT-2102): FT-2102 will be given in accordance with dosing schedule × 28 days out of 28 days. On C1D1 only a single dose of FT-2102 is taken.

[r] Combination agent (FT-2102 + azacitidine): azacitidine will be administered via subcutaneous injection or intravenous infusion in combination with oral FT-2102 for 7 days, and then azacitidine will be stopped for 21 days; a 48-hr dose interruption of the azacitidine for weekends or holidays is allowed. On all days and cycles when FT-2102 and azacitidine are co-administered, it is recommended to dose FT-2102 prior to azacitidine.

[s] After a patient discontinues study treatment and has completed their last study treatment visit, the study site may contact the patient approximately every 3 months to collect survival data and data pertaining to any other alternative anti-neoplastic therapy the patients begins for up to 12 months from the time of their 1st dose of study drug for the Phase 1 part of the study and up to 36 months for the Phase 2 part of the study. Patients who discontinue for reasons other than disease progression or who withdraw consent will continue to be followed for response until progression occurs.

Appendix 3 ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken et al. 1982.

Appendix 4 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03

The NCI CTCAE version 4.03 can be found by going to the following web site:

http://ctep.cancer.gov/reporting/ctc.html

Copies of the spiral-bound book of the NCI CTCAE Version 4.03 have been obtained from CTEP/DCT/NCI and are on file for AE classification by site clinical trial, nursing and medical staffs and in the Sponsor's clinical and data management offices.

Inquiries specifically regarding the Common Toxicity Criteria (CTC) should be addressed to: **ncictephelp@ctep.nci.nih.gov**

Appendix 5 NYHA Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 6 Drugs that are Generally Accepted by Authorities to have a Risk of Causing Torsades de Pointes

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval. Medications that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. Additional information can be found at: https://crediblemeds.org/index.php

Drugs	
Amiodarone	Ibutilide
Anagrelide	Levofloxacin
Arsenic trioxide	Levomepromazine (Only on Non US Market)
Astemizole (Removed from Market)	Levomethadyl acetate (Removed from Market)
Azithromycin	Levosulpride (Only on Non US Market)
Bepridil (Removed from Market)	Mesoridazine (Removed from Market)
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Cilostazol	Ondansetron
Ciprofloxacin	Oxaliplatin
Cisapride (Removed from Market)	Papaverine HCl
Citalopram	Pentamidine
Clarithromycin	Pimozide
Cocaine	Probucol (Removed from Market)
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone (Only on Non US Market)	Quinidine
Donepezil	Roxithromycin (Only on Non US Market)
Dronedarone	Sevoflurane
Droperidol	Sotalol
Erythromycin	Sparfloxacin (Removed from Market)
Escitalopram	Sulpiride (Only on Non US Market)
Flecainide	Sultopride (Only on Non US Market)
Fluconazole	Terfenadine (Removed from Market)
Gatifloxacin (Removed from Market)	Terlipressin (Only on Non US Market)
Grepafloxacin	Terodiline (Only on Non US Market)
Halofantrine	Thioridazine
Haloperidol	Vandetanib
Ibogaine (Only on Non US Market)	

Source: www.AZCert.org accessed 13 March 2017

Appendix 7 Response Criteria for AML

Adapted from IWG Response Criteria (Cheson et al. 2003); see also Stein et al. 2017.

Response Category	Response criteria (no minimum duration required unless indicated)
Morphologic leukemia free state (MLFS)	• BM blasts < 5% (in aspirate with spicules and 200 nucleated cells) • No blasts with Auer rods • No extramedullary disease
Morphologic complete remission (CR)	Same as MLFS, and: • ANC ≥ 1000/µL • Platelets ≥ 100,000/µL • Transfusion Independence
Cytogenetic Complete Remission (CRc)	CR with no residual cytogenetic abnormalities[a]
Molecular Complete Remission (CRm)	CR with undetectable IDH1m minimal residual disease (MRD)
CR with incomplete hematologic recovery (CRi)	CR but with ANC < 1000/µL, or platelets < 100,000/µL
CR with partial hematologic recovery (CRh)	< 5% BM blasts and partial recovery of peripheral blood counts (platelets > 50 x 10^9/L and ANC > 0.5 x 10^9/L)
Partial remission (PR)	Reduction of BM blasts: • to a value between 5 % – 25%, if baseline was ≥ 50% • by 50% to a value >5%, if baseline was between 5% - 49% Persistence of Auer rods, even if BM blasts ≤ 5% Hematologic values consistent with a CR: • ANC ≥ 1000/µL and • Platelets ≥ 100,000/µL
Stable Disease (SD)	Failure to achieve at least a PR but not meeting criteria for progressive disease (PD). SD for a period of 8 weeks or more indicates clinical benefit

Response Category	Response criteria (no minimum duration required unless indicated)
Recurrence, Morphologic Relapse	In patients who achieved CR, CRh, CRi, MLFS: • Reappearance of peripheral blasts, or • ≥ 5% BM blasts (if no peripheral blasts, may repeat BM assessment to distinguish relapse from BM regeneration) • Development of extramedullary disease
Disease Progression	In patients with PR or SD: • For patients with 5% to 66% BM blasts at nadir, a >50% increase in BM blast count percentage from the nadir and percentage is ≥ 20%; and • For patients with ≥ 67% BM blasts at nadir, a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count >10 x 10^9/L • New extramedullary disease

BM = bone marrow

[a] Analysis by either conventional banded karyotyping or FISH is accepted

Appendix 8 Response Criteria for MDS

Adapted from IWG Response Criteria for MDS (Cheson et al. 2006)

Response Category	Response criteria (responses must last at least 4 wks)
Complete remission (CR)	• Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted* • Peripheral blood‡: o Hgb ≥ 11 g/dL o Platelets ≥ 100×10^9/L o Neutrophils ≥ 1.0×10^9/L o Blasts 0%
Partial remission (PR)	All CR criteria if abnormal before treatment except: • Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% • Cellularity and morphology not relevant
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment Peripheral blood: if HI responses, they will be noted in addition to marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Relapse after CR or PR	At least 1 of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets • Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence

Response Category	Response criteria (responses must last at least 4 wks)
Disease progression (PD)	For patients with: • Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts • 5%-10% blasts: ≥ 50% increase to > 10% blasts • 10%-20% blasts: ≥ 50% increase to > 20% blasts • 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hgb by ≥ 2 g/dL • Transfusion dependence

HI: hematologic improvement

*Dysplastic changes should consider the normal range of dysplastic changes.

‡ Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Modified International Working Group Response Criteria for Hematologic Improvement

Hematologic improvement*	**Response criteria (responses must last at least 8 wks)**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wks compared with the pretreatment transfusion number in the previous 8 wks. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
Platelet response (pretreatment, < 100 X 10^9/L)	Absolute increase of ≥ 30 × 10^9/L for patients starting with ≥ 20 × 10^9/L platelets Increase from < 20 × 10^9/L to > 20 × 10^9/L and by at least 100%
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase > 0.5 × 10^9/L
Progression or relapse after HI‡	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥ 1.5 g/dL • Transfusion dependence

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy, gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Appendix 9 Drugs that are Strong Inducers or Sensitive Substrates of CYP3A4

Strong Inducers: Carbamazepine, rifampin, ritonavir, enzulatamide, mitotane, phenytoin, phenobarbital and St. John's wort

Sensitive Substrates: Alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Additional information can be found at:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1