Clinical Study Protocol

Protocol Title:	A phase 1, multi-center, open-label, single-arm, dose-escalation, clinical study to evaluate the safety, tolerability, pharmacokinetics (PK) and anti-tumor activity of FN-1501 monotherapy in patients with advanced solid tumors or relapsed/refractory Acute Myeloid Leukemia (AML)
Protocol Number:	FN-1501-UP1
Investigational Drug:	FN-1501
Sponsor:	Shanghai Fosun Pharmaceutical Development Co., Ltd.
Version:	Amendment 4
Version Date:	August 21, 2019

CONFIDENTIAL

Signature of the Sponsor's medically responsible person

The signatories agrees to the content of the final clinical study protocol as presented.

Name: Viviana Bozón, MD Role: Chief Medical Officer, US/Ex-China

Date: 21 · AUG · 2019 Signature:

Name: Ai-Min Hui Role: Global Chief Medical Officer

Date: 2019.8.23 Signature:

Signature of the Investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name: _____ Study site: _____

Date: _____ Signature: _____

PROTOCOL AMENDMENT, VERSION 4

Amendment rationale

Protocol FN-1501-UP1 is updated:

- Inclusion criteria: To clarify that laboratory requirements for complete blood counts (hemoglobin, ANC, and platelets) do not apply to AML patients.
- To clarify the maximum number of patients per cohort from six to four: "Additional patient(s), up to a maximum of four (4) patients in total, may be enrolled in a cohort if more than three (3) have been screened and are eligible for the cohort."
- Clarified that PK samples are taken "prior to that days dose (if applicable)"
- Moved in text reference citations to references (Section 13).
- Updated abbreviations and other typographical edits.
- Added signature for Ai-Min Hui, Global Chief Medical Officer

Section 7.1.3 (Electrocardiogram), updated text to match footnotes from Table 2.

Section 7.1.4 (Computed Tomography), clarified that CT scans do not apply to patients with AML.

Section 7.4 (Efficacy), to provide details for bone marrow biopsy and related assessments for patients with AML, added the following: Under amendment rationale for Version 3, "add the specific population" was revised to read "AML".

To include in the bone marrow assessments:

- Bone marrow cellularity
- Total cells counted
- Blasts in marrow
- Classical cytogenetic analysis

PROTOCOL AMENDMENT, VERSION 3

Amendment rationale

Protocol FN-1501-UP1 is updated:

- To include patients with relapsed/refractory Acute Myelocytic Leukemia (AML)

  Rationale in Acute Myeloid Leukemia:

  Patients with AML have a clear need for new therapeutic options. Preclinical data from in vivo studies suggest that FN-1501 as a single agent could offer cancer patients clinical benefit by inhibiting multiple tyrosine kinases including FMS-like tyrosine kinase 3 (FLT3), mutations of which are associated with leukemic transformation, and are present in up to 30% of this patient population.

  Considering that AML is not an ideal for a first in human study due to its rapid natural history and the risk of under-dosing the patients leading to rapid progression, the first in human study of FN-1501 only included patients with histologically or cytologically confirmed advanced solid tumors. Currently, this ongoing clinical trial has treated 9evaluable patients with solid tumors that completed the dose limiting toxicity (DLT) period in three cohorts of ascending doses, including 2.5 mg, 5.0 mg, and 10 mg. Cohort 4 at 15 mg is on-going. No DLTs have been reported.

  As the ongoing study is approaching the expected efficacious range for FN-1501, which has been estimated at 15-30 mg daily (based on preclinical data), we are amending the protocol to include the target patient population (AML) in the Study FN1501-001. Patients with AML that have no standard therapeutic options enrolled in this clinical trial will not be treated at sub-therapeutic doses and patients may receive clinical benefit since an active dose is expected.

- To modify the life expectancy of enrolled patients to at least three months

- To modify dose escalation rules. Increases of doses of FN-1501 will be set at 33% after 30 mg/day dose to have a traditional escalation scheme with meaningful change (currently the dose escalation is 16%) until the maximum tolerated dose (MTD) is reached

- To include a pharmacokinetic (PK) sample at steady state on Day 1 of Cycle 2
- To add DLT definitions for patients with AML
- To include evaluation criteria for patients with AML
- To modify the frequency of evaluation criteria for patients with solid tumors to every 6 weeks to align with the study-drug treatment schedule
- To include bone marrow biopsy in patients with AML
- To clarify electrocardiogram (ECG) procedures

PROTOCOL AMENDMENT, VERSION 2.2

Amendment rationale

Protocol FN-1501-UP1 is updated:

- To clarify serious adverse event (SAE) report procedure
- To revise wording for clarity and consistency

Changes to the protocol

- Sentence was added in Section 7.1.1 Local Laboratory Evaluation to specify that PI is responsible to assess lab test results.
- PK sampling schedule for additional PK was added in Section 7.5 Pharmacokinetics.
- "(usually involving at least an overnight stay)" was removed from Section 9.2 Definition of a SAE to include SAE without overnight stay.
- Section 9.8.2 Completion and Transmission of the SAE Report was updated to specify that the primary SAE report method is through an electronic case report form (eCRF) system, instead of paper form.
- Other editorial changes.

PROTOCOL AMENDMENT, VERSION 2.1

Amendment rationale

Protocol FN-1501-UP1 is updated:

- To clarify safety monitoring terms and procedure
- To specify the time window for assessments
- To revise wording for clarity and consistency

Changes to the protocol

- "Subject" was changed to "patient" through the protocol.
- Section 1.1 Background and Pharmacology was updated.
- Section 4.1.3 Study Procedure was added to separate some content from Section 4.1.2.
- Table 2 was updated; time windows for PK sampling, ECG and vital sign were added after Table 3.
- The sentence about pregnancy test results was changed to "The results of pregnancy texts will be recorded in the database" in Section 7.2.2.1 Pregnancy testing.
- AE/SAE causality categories were added in Section 9.6.2.
- Other editorial changes

PROTOCOL AMENDMENT, VERSION 2

Amendment rationale

Protocol FN-1501-UP1 is updated:

- to revise DLT definition for clarity
- to revise inclusion/exclusion criteria for clarity
- to specify study stopping criteria
- to specify treatment delay/interruption rule
- to specify DLT criteria for liver toxicity
- to add serum amylase and lipase tests

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version.

Synopsis:

- Revised inclusion criteria #3 to "Patients with histologically or cytologically confirmed advanced solid tumors who have relapsed or refractory disease for which no standard therapies expected to produce clinical benefit to the patient are available".
- Revised inclusion criteria #10 to "Men who are engaging or plan to engage in sexual activity with a female of childbearing potential must either have a prior vasectomy or agree to use effective contraception such as condoms, sexual abstinence, or appropriate methods taken by partner during the study and for 90 days after the last dose"
- Revised exclusion criterion #20 to "On medications that are strong cytochrome P450 (CYP)3A inhibitors or inducers unless patients are willing

and able to change to use of an equivalent medication that is not a strong CYP3A inhibitor or inducer".

Section 4.1.1: Dose Escalation

- Removed "The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the study unjustifiable." And re-wrote it in Section 4.1.3.
- Replaced "DLT is any adverse effect attributable to study drug that meets the following criteria, as determined by investigators based on NCI-CTCAE Version 4.03" with the following "DLT is any adverse event not attributable to disease or disease-related processes that occur during the DLT observation period. DLT is determined by investigators based on NCI-CTCAE Version 4.03".
- Replaced "Abnormal liver function test results defined as AST/ALT ≥ 3 ULN and total bilirubin ≥ 2 ULN for subject without liver metastasis" with the following: "For elevations in hepatic function enzymes, DLT is defined as follows:
    - Grade 4 AST or ALT increase
    - AST or ALT > 5 x ULN if accompanied by ≥ Grade 2 elevation in bilirubin
    - AST or ALT > 5 x ULN lasting > 3 days in patients without liver metastases
    - AST or ALT > 5 x ULN lasting > 3 days if the baseline value was ≤ 3 x ULN in patients with liver metastases
    - AST or ALT > 8 x ULN lasting > 3 days if the baseline value was > 3 x ULN but < 5 x ULN in patients with liver metastases"

Section 4.1.2: Continuous Treatment

- Updated Table 2: Study Assessment and Procedure Schedule.

Section 4.1.3: Study Stopping Rules

- Added a section to specify study stopping rules.

Section 4.2.1: Inclusion Criteria

- Revised inclusion criteria #3 and #10 for consistency with the synopsis.

Section 4.2.2: Exclusion Criteria

- Revised exclusion criterion #20 for consistency with the synopsis.

Deleted original Section 4.2.4: Dose Adjustment

Section 4.2.5: Subject Completion and Discontinuation became Section 4.2.4

- Updated Section 4.2.4.2: Subject Discontinuation and added the following paragraph "A subject must be discontinued if any one or more of the conditions occur: 1) DLT occurs and the toxicity is not improved to Grade 1, Grade 0 or baseline within 14 days of onset; 2) occurrence of other toxicities that makes continuation of study treatment intolerable; 3) a third dose-reduction is required; 4) treatment delay is more than 4 weeks, unless resuming treatment is regarded beneficial to the subject by the investigator and agreed by Sponsor's medical monitor; 5) in the opinion of the investigator, continuous treatment is not beneficial to the subject."

Section 5.2.1: Dose Delays and Modifications

- Added a section to specify dose delays and modifications.

Section 7.1.1: Local Laboratory Evaluation

- Added serum amylase and lipase tests in Table 6. Clinical Laboratory Assessment.

Appendix 1: Signature of Investigator

- Updated protocol title for consistency

Synopsis

Title:	A phase 1, multi-center, open-label, single-arm, dose-escalation, clinical study to evaluate the safety, tolerability, pharmacokinetics (PK) and anti-tumor activity of FN-1501 monotherapy in patients with advanced solid tumors or in relapsed/refractory Acute Myeloid Leukemia (AML)
Investigational drug:	FN-1501 lyophilized powder
Protocol No.	FN-1501-UP1
Clinical phase:	Phase 1
Number of patients:	Estimated 33 evaluable patients
Number of sites and locations:	3 sites in the United States (US) and Australia
Study cycle:	Screening period: Day -21 to Day -1. Treatment period: In the first cycle, a single dose of study drug will be administered three times a week on Days 1, 3, 5, 8, 10, and 12, with the last week off study drug (total 21 days). Subsequent treatment cycles will be 21 days and the study drug will be administered with the same dose and the same schedule as the first cycle. Follow-up period: 30 days after the last dose.
Objectives	
Primary	To evaluate the safety and tolerability of FN-1501 To determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D)
Secondary	To characterize the PK of FN-1501 and major metabolites To describe the preliminary anti-tumor activity of FN-1501
Study design: This is a phase 1, first-in-human, open-label, multi-center, single-arm, dose escalation clinical study in patients with histologically or cytologically confirmed advanced solid tumors or relapsed/refractory AML, who cannot tolerate or do not respond to standard systemic therapy. It aims to determine the MTD and RP2D, evaluate the safety, tolerability, PK characteristics, and the preliminary anti-tumor activity of FN-1501.	

Eligible patients will receive a single intravenous infusion of study drug on Days 1, 3, 5, 8, 10, and 12 of a 21-day cycle. Dose limiting toxicity (DLT) assessment period is the first cycle of study treatment.

Starting dose, dose escalation scheme, and stopping criteria

- Dosing will begin at 2.5 mg once per day on the assigned days.
- Dose escalation will use the traditional 3+3 design and follow a modified Fibonacci sequence until MTD is reached. Increments of 33% in the dose of FN-1501 will be undertaken after reaching 30 mg/day. Because of the dosage form (10 mg/vial), each dose will be rounded up or down to levels such as 2.5, 5, 10, 22.5 mg/day, etc. At least 3 patients will be enrolled in each cohort. Dose escalation or de-escalation will be determined by the number of DLTs in each cohort.
- The highest dose under which one or no case of DLT is observed will be considered as MTD. If DLT cannot be observed, RP2D will be determined based on safety, preliminary anti-tumor activities and PK data.
- Additional patients will not start the treatment until 48 hours after the 1st dosing of the 1st patient in the same cohort.
- Approximately thirty-three patients are expected to be enrolled.

Continuous Treatment: A continuous treatment cycle is defined as 3 times a week for 2 weeks followed by 1-week rest. Each cycle is 21 days. Administration of FN-1501 will be continued until disease progression, intolerable toxicity, withdrawal of consent, or termination according to the Principal Investigator's judgment or at the sponsor's request.

Population:	Patients with histologically or cytologically confirmed advanced solid tumors or relapsed/refractory AML, who cannot tolerate or do not respond to standard therapies, or for whom no standard therapy exists.
Inclusion criteria:	Each patient must meet all the inclusion criteria for this study at the time of initial treatment: 1. Male and female 18 years old and above 2. Able to understand and sign informed consent form 3. Patients with histologically or cytologically confirmed advanced solid tumors who have relapsed or refractory disease or relapsed/refractory AML for which no standard therapies expected to produce clinical benefit to the patient are available

	4. Patients with diagnosed solid tumors must have at least one lesion that is measurable per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria 5. Patients with relapsed or refractory AML must be diagnosed with AML based on World Health Organization (WHO) criteria (≥ 20% blasts in bone marrow). Patients with acute promyelocytic leukemia are excluded 6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 7. Have discontinued all previous cancer therapies for at least 21 days (for solid tumors) or at least 7 days (for AML) or 5 half-lives prior to study treatment, whichever is shorter, and recovered from the acute adverse effects of therapy 8. Expected to survive at least 2 to 3 months 9. Left ventricular ejection fraction (LVEF) ≥ 50% and QTc interval < 450 ms 10. Women shall meet either of the following conditions before enrollment - Infertile (see Section 4.2.1) - For those of childbearing potential, they should have a negative serum pregnancy test during the screening, agree to refrain from lactation, and use effective contraception such as hormonal methods associated with inhibition of ovulation, condom, intra-uterine device, surgical sterilization (including partner's vasectomy) or sexual abstinence during the study and for 30 days after the last administration of study drug 11. Men who are engaging or plan to engage in sexual activity with a female of childbearing potential must either have a prior vasectomy or agree to use effective contraception such as condoms, sexual abstinence, or appropriate methods taken by their partner(s) during the study and for 90 days after the last dose

	12. Patients must have adequate organ functions as indicated by the following screening laboratory values: - Serum total bilirubin ≤ 1.5 × upper limit normal (ULN) (Serum total bilirubin can be ≤ 3.0 × ULN if patients have hemolysis or congenital hemolytic diseases) - Creatinine < 1.5 × ULN or estimated creatinine clearance ≥ 50 mL/min - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN (AST and ALT can be ≤5 × ULN for patient with liver metastases) - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L - Platelets ≥ 100 × 10^9/L - Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (Note: Criteria must be met without a transfusion within 2 weeks of obtaining the sample) **Note:** Laboratory requirements for complete blood counts (hemoglobin, ANC, and platelets) do not apply to AML patients
Exclusion criteria:	Patients who meet any of the following exclusion criteria are not eligible to participate in this study: 1. Participation in another therapeutic clinical trial within 3 weeks of enrollment 2. A previous toxicity-related reaction towards cancer therapy have not recovered within 2 weeks of enrollment (>Grade 2 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03) 3. Having received a major surgical operation within 4 weeks of enrollment or not yet completely recovered from a previous operation 4. Any serious or uncontrollable systemic disease, including but not limited to: Hypertension (after treatment, systolic blood pressure (SBP) > 180 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg) and active hemorrhagic

	disorders; patients who are determined by investigators as otherwise not suitable for participation in this study. Note: Patients that in the judgment of the investigator have clinical signs of disease progression during the screening period (i.e.: febrile neutropenia, ascites requiring drainage, hospitalization due to worsening underlying disease, etc.) will not be eligible for participation. 5. Active known infection, including hepatitis B, hepatitis C, and human immunodeficiency virus 6. Primary central nervous system (CNS) tumor or CNS metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with a history of CNS metastases or cord compression are allowable if they have been definitively treated and have been clinically stable for at least 3 months, and off steroids or anticonvulsants ≥ 2 weeks before first dose of study drug) 7. Serious kidney injury, requiring dialysis 8. Serious liver injury, and advanced liver diseases of Child-Pugh class B and C 9. On medications that are strong cytochrome P450 (CYP)3A inhibitors or inducers unless patients are willing and able to change to use of an equivalent medication that is not a strong CYP3A inhibitor or inducer 10. Cardiac function and disease history which meets one or more of the following conditions: - Any risk which may increase QTc interval prolongation, such as hypokalemia, hereditary long QT syndrome and taking drugs that can prolong QT interval - Acute myocardial infarction ≤ 6 months prior to Day 1 - Clinically significant arrhythmia ≤ 6 months prior to Day 1

	- Congestive heart failure ≥ Grade 3 by New York Heart Association (NYHA) ≤ 6 months prior to Day 1 - Cerebral vascular accident (CVA) ≤ 6 months prior to Day 1 11. Are pregnant or breastfeeding
Investigational drug and dosage and administration	FN-1501 lyophilized powder Strength:10 mg/vial Possible dose levels: 2.5, 5, 10, 15, 22.5, 30, and 40 mg per day. Administration: 10 mg/vial FN-1501 will be diluted in 10 mL 5% glucose and added in 100 mL 5% glucose for intravenous infusion. Intravenous infusion should be completed within 1 hour.
Reference therapy	Not applicable

Criteria for Evaluation:

Primary Endpoints

The safety of FN-1501 will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events (SAEs) per the NCI CTCAE Version 4.03, physical examination, and laboratory measurements.

The MTD of FN-1501 will be the highest dose under which one or no case of DLT is observed while the RP2D of FN-1501 will be determined based on PK, safety and tolerability, and preliminary efficacy.

Secondary Endpoints

Blood sample collection:

- Cycle 1 Day 1: pre-dose, post dose 5, 15, 30 minutes, 1, 2, 4, 6, 8, 12, 24, and 48 hours, and on Day 8 prior to that days dose (if applicable)

PK for a single dose profile: area under the plasma concentration-time curve from zero to the last measurable concentration ($AUC_{0\text{-last}}$), area under concentration-time curve from 0 to 24 hours ($AUC_{(0\text{-}24)}$), area under concentration-time curve from 0 to infinity ($AUC_{0\text{-}\infty}$), maximum plasma concentration (C_{max}), the time to reach maximum concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent volume of distribution (V_d), linear index (LI), and clearance (CL).

Anti-tumor activity: Complete response (CR), partial response (PR), stable disease (SD), progression-free survival (PFS), and duration of response for patients with solid tumors.

Morphologic leukemia-free state in patients with AML.

Statistical Method

It is anticipated that approximately 33 patients will be required to establish the RP2D(s) of FN-1501.

All patients who are exposed to FN-1501 will be included in the safety population. All patients who have at least one measurable concentration and for whom valid PK parameters can be estimated will be included in the PK population.

Data will be listed and summarized according to the reporting standards chosen by the sponsor.

Table of Content

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List of Abbreviations and Definition

Abbreviation	Definition
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
Ara-c	Cytarabine
AST	Aspartate Aminotransferase
AUC	Area Under Plasma Concentration-time Curve
$AUC_{0\text{-}24}$	AUC from 0 to 24 hours
$AUC_{0\text{-}\infty}$	AUC from zero to infinity
$AUC_{0\text{-last}}$	AUC from zero to the last measurable concentration
BMI	Body Mass Index
CDK	Cyclin-dependent Kinase
CERT	Center for Education and Research on Therapeutics
CL	Clearance
C_{max}	maximum observed plasma concentration
CNS	Central Nervous System
CR	Complete Response
CRO	Clinical Research Organization
CT	Computed Tomography
CVA	Cerebral Vascular Accident
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
HED	human equivalent dose
hERG	human ether-a-go-go-related
HSC	hematopoietic stem cells
IB	Investigator's Brochure

Abbreviation	Definition
IC_{50}	50% Inhibition Concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITD	internal tandem duplication
JM	Juxtamembrane Domain
LI	Linear Index
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall Survival
PD(s)	Pharmacodynamic(s)
PDGFR	Platelet-derived Growth Factor Receptor
PFS	Progression-Free Survival
PK(s)	Pharmacokinetic(s)
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP(s)	Standard Operating Procedure(s)
$t_{1/2}$	Terminal half-life
TLS	Tumor Lysis Syndrome
t_{max}	time to maximum observed plasma concentration
ULN	Upper Limit of Normal
US	United States
V_d	Apparent Volume of Distribution
V_{dss}	Apparent Volume of Distribution at Steady State
WHO	World Health Organization

Abbreviation	Definition

1. Introduction

1.1 Background and Pharmacology

Receptor tyrosine kinases (RTK), a group of transmembrane proteins, are responsible for growth factor signaling transduction in normal cellular functions. Abnormal RTK functions are associated with human tumorigenesis [1]. FMS-like tyrosine kinase 3 (FLT3) belongs to the type III receptor tyrosine kinase family and plays a well-established role in normal growth and differentiation of hematopoietic precursor cells [2]. FLT3 mutations have been reported to occur in approximately 30% newly diagnosed acute myeloid leukemia (AML) patients. Internal tandem duplications (ITD) in FLT3 is the most frequent mutation in AML and correlated with more aggressive progress and poor prognosis [3].

FN-1501 is an inhibitor of various tyrosine kinases such as cyclin-dependent kinase 4/6 (CDK4/6), platelet-derived growth factor receptor (PDGFR), KIT protein, anaplastic lymphoma kinase (ALK) and RET protein, particularly potent on FLT3. The preclinical data generated from biochemical, cell based and animal in vivo studies suggest that FN-1501 could offer cancer patients clinical benefit by inhibiting multiple tyrosine kinases including FLT3, PDGFR, KIT, ALK, RET, etc.

In vivo studies demonstrated that FN-1501 effectively reduced the tumor size of MV-4-11 and MOLM-13 (models with FLT3/ITD mutation), as well as inhibited the growth of Jurkat and clone E6-1 human leukemia subcutaneous xenotransplanted tumor in nude mice in a dose-dependent manner. FN-1501 also significantly inhibited the growth of colon cancer cells in animal models.

FN-1501 levels in plasma and tumor tissue collected from MV-4-11 tumor bearing mice after single intravenous injection at the effective dose in an efficacy study showed favorable correspondence with the inhibition of STAT5 phosphorylation, indicating a good pharmacokinetic (PK)/pharmacodynamic (PD) efficacy relationship. According to nonclinical PD data in nude mice models MV-411 and MOLM-13, the effective dose of FN-1501 in inhibiting subcutaneously implanted tumor was 2.5-5 mg/kg, which is equivalent to a human dose of 12.5-25 mg. Hence the estimated efficacious dose range in humans is between 12.5 and 25 mg/day.

Please refer to the Investigator's Brochure (IB) for more detailed information on the background of FN-1501.

1.2 Pharmacokinetics

FN-1501 showed wide distribution volume and fast plasma clearance (CL) in in vivo studies. In plasma protein binding assays using mouse, rat, dog, monkey, and

human plasma, FN-1501 exhibited a moderate binding (≥50% and <95.0%) to plasma proteins in all 5 species within the range of 0.2 μM to 10 μM. No drug accumulation was observed after 7-day consecutive intravenous injection at 3.64 mg/kg/day in rats or at 0.456 mg/kg in monkeys.

After single intravenous slow injection at 1.21, 3.64, and 7.28 mg/kg to Sprague-Dawley rats, FN-1501 showed the maximum observed plasma concentration (C_{max}) values of 197 ± 70.7, 580 ± 42.8, and 1510 ± 291 ng/mL, respectively, and plasma CL of 117 ± 17.1, 139 ± 19.6, and 98.5 ± 11.0 mL/min/kg, respectively. Apparent volume of distribution at steady state (Vdss) was 22.0±7.51, 21.9±1.84, and 17.8±4.01 L/kg, respectively, and terminal half-life ($t_{1/2}$) was 2.82 ± 0.749, 2.51 ± 0.0817, and 3.01 ± 0.469 hours, respectively. Following single intravenous slow injection administration of FN-1501 at 0.152, 0.456, and 0.912 mg/kg in cynomolgus monkeys, C_{max} appeared immediately after infusion. The C_{max} values were 263±62.2, 780±51.4, and 1480±164 ng/mL, respectively; CL was 42.3±5.40, 34.8±5.68, and 28.4±4.04 mL/min/kg, respectively; the Vdss was 5.88±1.20, 8.58±1.60, and 9.18±1.91 L/kg, respectively; $t_{1/2}$ was 2.40±0.286, 4.56±1.88, and 6.77±1.96 h, respectively.

After single intravenous slow injection at 3.64 mg/kg to Sprague-Dawley rats, FN-1501 distributed to all tissues within 15 minutes. The highest tissue exposure area under plasma concentration-time curve $(AUC)_{0\text{-last}}$ was observed in spleen.

A total of 8 drug metabolites were identified in liver microsomes of mouse, rat, dog, monkey, and humans after incubation with FN-1501 at 37°C for 60 minutes. The four metabolites detected in human liver microsomes were all found in monkey liver microsomes, suggesting that no unique metabolites were formed in human liver microsomes. Among the four metabolites detected in human liver microsomes, three (M4, M5, M7) were in low level while M3 was 16.89% of total drug. FN-1501 was mainly metabolized via oxidation and N-demethylation. cytochrome P450 (CYP)3A was the major metabolic enzyme; other CYP isozymes played minor or no role in the metabolism of FN-1501.

FN-1501 was mainly excreted through feces and urine. Following single intravenous slow injection of FN-1501 at 3.64 mg/kg to male and female Sprague-Dawley rats, the gender averaged drug recovery of FN-1501 from feces and urine at 120 hours post dose was 54.4 ± 9.55% of nominal dose, and feces was the main excretion pathway. The gender averaged drug recovery of FN-1501 from bile at 72 hours post dose was 18.2 ± 5.55% of nominal dose.

Please refer to the IB for more detailed information on the PK of FN-1501 [4].

1.3 Toxicology

The non-clinical toxicity profile of FN-1501 was characterized in both rats and monkeys in single and repeat dose studies up to 28 days, and in a core battery of genotoxicity tests, including in vitro Ames and chromosomal aberration assays, and an in vivo bone marrow micronucleus assay in mice.

FN-1501 related pathological changes in rats include weakness, eye discharge, squint, reduced spontaneous motor activities, reduced body weight and body weight gain, lacrimation, sparse hair, macropathological ulcer and swelling on skin, decreased blood cell count and histological ulcer and swelling of dermatitis. Possible test article-related pathological changes were osteosclerosis in bone marrow (femur and sternum), basophilic tubule in kidney, and atrophy in thymus. The maximum tolerated dose (MTD) was 15 mg/kg in a repeated-dose toxicity study and the lethal dose was 40 mg/kg in an acute toxicity study in rats.

FN-1501 related pathological changes in monkeys included erythema and edema at injection sites, foot ulcer, and decreased blood cell count. Possible test article-related pathological changes were small thymus, thymus atrophy, and necrosis. The MTD of FN-1501 in monkeys was 10 mg/kg in an acute toxicity study and 2 mg/kg in a 28-day repeated-dose study.

The study on human ether-a-go-go-related (hERG) current showed that FN-1501 inhibited hERG current of HEK-293 cells, wherein 50% inhibition concentration (IC_{50}) was 2.870 μM.

FN-1501 transiently and mildly elevated diastolic blood pressure (DBP) and mean arterial blood pressure at the dosage of 2 and 4 mg/kg and decreased body temperature at the dosage of 4 mg/kg. There were no effects on electrocardiogram (ECG) parameters at any dose level in this study.

No mutagenicity or genotoxicity was detected in the absence and presence of a metabolic activation system.

Refer to the IB for more detailed information on the toxicity of FN-1501 [4].

1.4 Rationale in Acute Myeloid Leukemia

AML accounts for about 80% of adult acute leukemia cases, with an incidence of 3-5/100,000 in the United States (US). The incidence of AML increases with age. For example, the incidence of AML increases from 1.3/100,000 in those under 65 to 12.2/100,000 in those 65 and above. The "3+7" induction chemotherapy, i.e., 1-2 cycles of the standard-dose of cytarabine (Ara-c) in combination with anthracyclines (rubidomycin, daunorubicin, etc.) is the recommended first line treatment for AML, which exhibits a complete remission rate of higher than 80%, then followed by the

consolidation chemotherapy (1-3 cycles of Ara-c). The 5-year overall survival (OS) can reach 40-50% with this regimen. However, after being treated with the "3+7" treatment scheme for 1-2 cycles, 10% to 40% of patients with AML fail to achieve complete response (CR) or relapse within six months after the first CR. No drug has yet been approved by the Food and Drug Administration (FDA) in treatment of recurrent/refractory AML and clinical trials are strongly recommended. Currently, the only treatment option is incremental dose of Ara-c or combination of multiple drugs, which bear non-significant efficacy in terms of remission rate and long-term OS benefit.

AML is caused by abnormal proliferation and differentiation of hematopoietic stem cells (HSC), characterized by clinical manifestations and significant biological heterogeneity. Nearly all (97%) of AML patients present molecular abnormality to a certain degree, FLT3 mutations are found in 30% of them [5]. FLT3 belongs to the Type III RTK family. FLT3 consists of four domains: 1) extracellular N-terminus including 5 immunoglobulin-like domains, is a ligand-binding site; 2) transmembrane domain; 3) intracellular juxtamembrane domain (JM) and 4) intracellular C--terminal kinase domain. When ligands bind to extracellular region, FLT3 receptors are dimerized, terminal kinase domain is activated to release the intracellular signaling molecules, and the growth and development of HSC are regulated through PI3K/AKT and MAPK signaling pathways. FLT3/ITD mutation is the most common FLT3 mutation, which accounts for about 20% of all FLT3 mutations. ITD mutation leads to non-ligand-dependent dimerization of FLT3, continuously activates intracellular signaling pathways, realizes non-cytokines-dependent cell proliferation and differentiation disorders thus results in leukemia. FLT3 point mutation can be found in 7%-10% AML patients, and its correlation with AML is not fully understood. At present, development of FLT3-ITD-targeted therapeutics is very active and FDA granted Breakthrough Therapy designation to Midostaurin in February 2016 and Priority Review status was granted in November 2016. In 2017, Midostaurin became the first potential AML targeted therapy approved by FDA. In their pivotal trial, midostaurin plus standard chemotherapy was superior to placebo plus standard chemotherapy in OS (HR 0.77; 95% CI 0.63, 0.95; 2 sided p = 0.016) [6].

FN-1501, a new investigational inhibitor of FLT3, may provide clinical benefit for patients in the treatment of relapsed or refractory AML with or without the presence of the FLT3 mutation.

1.4.1 Rational for Starting Dose Selection

A dose of 2.5 mg/day is selected as the starting dose in this study based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 [7] and results of toxicological studies. ICH S9 recommends that the starting dose should be 1/6th of MTD observed in non-

rodent studies. The MTD is calculated as 2 mg/kg from the 28-day repeated intravenous infusion toxicity study in monkeys. Using the conversion factors published in the FDA Guidance for Industry, *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (2005)* [8], the human equivalent dose (HED) derived from $1/6^{th}$ of the monkey MTD is 6.48 mg/d. However, considering FN-1501 as a novel API with limited toxicity data, we set the lower starting dose at $1/10^{th}$ of MTD calculated from the 28-days repeated toxicity study in monkeys, which is 3.88 mg/d. Because the strength of FN-1501 is 10 mg/vial and 3.88 mg/d is not convenient in clinical practice, we finally choose 2.5 mg (1/4 × 10 mg) as the safe starting dose for the First-in-Human clinical trial.

2 Study Objectives

2.1 Primary Objectives

To evaluate the safety and tolerability of FN-1501

To determine the MTD and recommended phase 2 dose (RP2D)

2.2 Secondary Objectives

To characterize the PK of FN-1501 and major metabolites

To describe the preliminary anti-tumor activity of FN-1501

3 Study Endpoints

3.1 Primary Endpoints

The safety of FN-1501 will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events (SAEs) [per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.3], physical examination, and laboratory measurements.

The MTD of FN-1501 will be the highest dose under which one or no case of dose limiting toxicity (DLT) is observed while the RP2D of FN-1501 will be determined based on PKs, safety and tolerability, as well as preliminary efficacy.

3.2 Secondary Endpoints

Blood sample collection:

Cycle 1 Day 1: pre-dose, post dose 5, 15, 30 minutes, 1, 2, 4, 6, 8, 12, 24, and 48 hours and on Day 8 prior to that days dose (if applicable)

PK for single dose profile:

AUC from zero to the last measurable concentration ($AUC_{0\text{-last}}$), AUC from 0 to 24 hours ($AUC_{0\text{-}24}$) , AUC from zero to infinity ($AUC_{0\text{-}\infty}$), C_{max}, time to maximum observed plasma concentration (t_{max}), $t_{1/2}$, CL, apparent volume of distribution (Vd), and Linear Index (LI).

Endpoints for anti-tumor activity evaluation

Anti-tumor activity will be evaluated by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (solid tumor), performance status, and Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) image at designated time point and time of event. Imaging for disease assessment will be performed every 6 weeks to summarize CR, partial response (PR), stable disease (SD), progression-free survival (PFS), and duration of response for patients with solid tumors.

In patients with AML, response will be evaluated according to the AML response criteria [5]. Bone marrow assessments will be performed at Screening, the end of every other cycle, and at the end of the study or at time of relapse.

Based on the patient's clinical condition, complete blood counts or bone marrow assessments may occur more frequently based on Investigator's judgment.

4 Investigational Plan

4.1 Summary of Study Design

This is a phase 1, first-in-human, open-label, multi-center, single-arm, dose escalation clinical study in patients with histologically or cytologically confirmed advanced solid tumors or relapsed/refractory AML, who cannot tolerate or do not respond to standard systemic therapy.

Patients will be screened for eligibility for up to 21 days prior to entry into the study. The starting dose will be 2.5 mg/day on the assigned days. Dose escalation will use the traditional 3+3 design and follow a modified Fibonacci sequence until MTD is reached. Increments of 33% in the dose of FN-1501 will be undertaken after reaching 30 mg/day. Eligible patients will receive a single intravenous infusion of study drug on Days 1, 3, 5, 8, 10, and 12 of a 21-day cycle.

The DLT assessment period is 21 days from the first dose of FN-1501. Evaluation of a cohort of at least three (3) patients completing DLT assessment at any given dose level is required prior to determining the next dose level and dose regimen for the subsequent cohort.

The highest dose under which one or no case of DLT is observed will be considered as MTD. If DLT cannot be observed, RP2D will be determined based on safety, preliminary anti-tumor activities and PK data.

Approximately thirty-three patients are expected to be enrolled.

After the first patient in the cohort receives the Cycle 1, Day 1 dose, subsequent patients in that cohort will not be dosed until the first patient has been evaluated for at least 48 hours to exclude unexpected acute toxicity. The continuous safety evaluation will be performed by investigators, the medical monitor, and the sponsor. A Safety Monitoring Committee (SMC) will determine dose levels to be administered and dose regimen during dose escalation based on the data available from the previous dose levels. If an MTD is not identified due to paucity of DLTs, the RP2D will be determined based on PKs, safety, tolerability, and preliminary efficacy.

If a patient wishes to continuously receive study treatment on completion of Cycle 1, the patient can continue study treatment in 21-day Cycle 2 and subsequent cycles (same as Cycle 2, all of 21 days' duration), defined as administration of 3 times per week for 2 weeks followed by 1 week rest, at the discretion of the investigator.

4.1.1 Dose Escalation

The DLT assessment period is 21 days starting from the first dose of FN-1501. The study will follow a standard 3+3 dose escalation scheme and a modified Fibonacci sequence until the MTD is reached. Increments of 33% in the dose of FN-1501 will be undertaken after reaching 30 mg/day. Because of the dosage form (10 mg/vial), each dose will be rounded to numbers such as 2.5, 5, 10, 15, 22.5 mg/day, etc. At least three (3) patients will be enrolled into each cohort.

Additional patient(s), up to a maximum of four (4) patients in total, may be enrolled in a cohort if more than three (3) have been screened and are eligible for the cohort.

The DLT assessment and dose-escalation scheme will follow the same principle as stipulated for a standard 3+3 dose escalation design. For example, one (1) to three (3) additional patients will be enrolled if a DLT is observed in one (1) of first three (3) patients. No additional patients are required if a DLT is observed in one (1) of six (6) patients.

The starting dose will be 2.5 mg/day administered on the assigned days. One possible dose escalation scheme is presented in Table 1. Other dose levels may be evaluated during the study, depending on emerging data.

Table 1: Suggested Dose Escalation Scheme

Dose Level/Cohort	Dose (mg/d)	Increase (%)
1	2.5	100
2	5	100
3	10	50
4	15	50
5	22.5	33
6	30*	33
7	40*	33

The actual dose levels and dose regimens administered in each step will depend on the data available from the previous level, as determined by the Safety Monitoring Committee.
* Increments of 33% in the dose of FN-1501 will be undertaken after reaching 30 mg/day until the MTD is reached.

As currently planned, if none (0) of the patients in one cohort experience DLT during the DLT assessment period, the dose to be administered in the next cohort will be increased by up to 100% (up to the 10 mg/d dose), by up to 50% (for the 10 mg and 22.5 mg doses) and by 33% thereafter, as determined by the SMC formed by the medical monitor, investigator, and sponsor representative.

The dose intervals will follow standard 3+3 escalation rules starting with the treatment of 3 patients as follows:

1. If 0 of 3 patients experiences a DLT, dose escalation will proceed to the next higher dose level at which 3 patients (up to 4) will be enrolled.
2. If 1 of 3 patients experiences a DLT, 3 more patients will be enrolled at the same dose level.
3. Escalation will continue if 0 or 1 of 6 patients experiences a DLT.
4. If 2 or more patients in any dose level experience a DLT, dosing will stop.

No additional patients will be treated at a given dose level if two (2) or more of the patients in the cohort develop a DLT during the DLT assessment period. In this instance, the MTD is considered to have been exceeded. If the MTD is exceeded, the next lower dose level is considered MTD. Depending on the decision of the SMC and on review of available data, an additional intermediate

dose level, between the MTD-exceeding dose level and the next lower dose level, may be explored. If an MTD is not identified due to paucity of DLTs, the RP2D will be determined based on PKs, safety, tolerability, and preliminary efficacy.

DLT Definition:

DLT is any AE not attributable to disease or disease-related processes that occur during the DLT assessment period. DLT is determined by investigators based on NCI-CTCAE Version 4.03:

Non-hematologic:

- Grade 3 or greater nausea, vomiting and diarrhea despite optimal supportive care
- Any other clinically relevant ≥ Grade 3 non-hematologic toxicity (excluding asymptomatic biochemical abnormalities that are not clinically significant and resolve to Grade 2 or less in <7 days)
- Persistent Grade 2 toxicity such as nausea, vomiting, or fatigue despite optimal standard medical therapy that, in the opinion of the investigator, prevents continuous dosing
- Any toxicity which in the judgment of the investigator or sponsor is dose limiting

Hematologic:

- Grade 4 neutropenia lasting > 7 days
- Grade 3 Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of 38.3^oC or a sustained temperature of 38^oC for > 1 hour)
- Grade 3 neutropenic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia

For elevations in hepatic function enzymes, DLT is defined as follows:

- Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increase
- AST or ALT > 5 × upper limit of normal (ULN) if accompanied by ≥ Grade 2 elevation in bilirubin
- AST or ALT > 5 × ULN lasting > 3 days in patients without liver metastases

- AST or ALT > 5 × ULN lasting > 3 days if the baseline value was ≤ 3 × ULN in patients with liver metastases
- AST or ALT > 8 × ULN lasting > 3 days if the baseline value was > 3 × ULN but ≤ 5 × ULN in patients with liver metastases

Specific DLT definitions for patients with AML:

Non-hematologic:

- All non-hematologic toxicities NCI-CTCAE ≥ Grade 3

Hematologic:

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

4.1.2 Continuous Treatment

At the discretion of the investigator, patients may receive continuous treatment, at the same dose, upon completion of the DLT assessment period until disease progression, intolerable toxicity, withdrawal of consent, or termination according to the Principal Investigator's judgment or at the sponsor's request. Continuous treatment is defined as administration 3 times per week for 2 weeks followed by 1-week rest in a repeating 21-day cycle.

4.1.3 Study Procedures

Study procedures are listed and described in Table 2. Detailed descriptions of the time points for PK sampling, ECG, and vital signs evaluations in the first week of Cycle 1 is included in Table 3.

Table 2: Study Assessment and Procedure Schedule

Assessment	**Screen period**	**Cycle 1 (21 days)**							**Subsequent cycles (21 days)**		**Follow-up/ End of Study**
Day of Cycle	**-21 to -1**	**1**[1]	**2**	**3**	**5**	**8**	**10**	**12**	**1**[2] **(±3)**	**8 (±3)**	**30 to 35 days post last dose**
Inform consent	X										
Review eligibility	X										
Demographic data	X										
Medical history/ baseline conditions	X										
Disease assessment Solid Tumors[3]	X	Every 6 weeks ± 5 days and as detailed in the footnote									
Disease Assessment AML[3]	X	Every 6 weeks ± 5 days and as detailed in the footnote									
Vital signs	X	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Weight	X	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Physical exam[5]	X	X[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
ECOG performance review	X	X[4]				X[4]			X[4]		X
12-lead ECG[6]	X	X							X		X
Concomitant medications review	X	X				X			X		X
CT or MRI (solid tumor only)	X[7]	Every 6 weeks ± 5 days									
Pregnancy test[8]	X	X							X		
Hematology[9]	X	X[4]				X[4]			X[4]	X[4]	X
Blood chemistry + amylase and lipase tests[9]	X	X[4]				X[4]			X[4]	X[4]	X

Assessment	**Screen period**	**Cycle 1 (21 days)**							**Subsequent cycles (21 days)**		**Follow-up/ End of Study**
Day of Cycle	**-21 to -1**	**1**[1]	**2**	**3**	**5**	**8**	**10**	**12**	**1**[2] **(±3)**	**8 (±3)**	**30 to 35 days post last dose**
Bone Marrow Biopsy for patients with AML[10]	X	Every 6 weeks ± 5 days and as detailed in the footnote									
Coagulation test[9]	X										X
Urinalysis[11]	X								X		X
Adverse event	X	X continuous									
PK blood sample		X	X	X[12]					X[12]		
Study drug[13] administration		X		X	X	X	X	X	X	X	

Abbreviations: AML = Acute Myeloid Leukemia; BMI = Body Mass Index; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PK = pharmacokinetic

1. On Day 1 of Cycle 1, patients may need to stay at the clinical research unit overnight to complete PK sampling, safety observation and assessments.
2. For DLT cycle, patients will return for the end of the DLT assessment period (21 days from first dose of FN-1501) assessments on Day 1 of Cycle 2 (±3 days). If additional cycles are planned, patients will start Day 1 dosing of next cycle after the assessments. For the last cycle, patients will return for the assessments.
3. Disease assessment every 6 weeks to coincide with every other cycle. Refer to Section 7.4 for details.
4. These assessments should be conducted, and the results should be available before study drug administration in each cycle. If assessments are conducted within 3 days prior to Day 1 of the cycle, the data can be recorded as Day 1 data of the cycle. See Table 3 for details. Height to be measured at Screening for BMI calculation.
5. A full physical exam will be conducted at screening, on Day 1 of each cycle and at follow-up. A full physical exam includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities. Refer to Section 7.1.2 for details.

6. ECGs to be performed prior to that days dose (if applicable) and after the patient has been supine for at least 10 minutes and should be performed with the patient in the same physical position for the duration of the test. ECG at Screening: performed in triplicate (5-10 min between readings). ECG at Day 1 of Cycle 1: performed in triplicate (5-10 min between readings) at the days indicated in Table 2 and time points and time windows detailed in Table 3. Cycle 2 Day 1: Perform in triplicate (5-10 min between readings) only if patient has a significant QTc prolongation, that is, a) > 500 msec; or b) increased by ≥ 60 msec over baseline; and/or c) decreased by 50 msec below pre-dose recording. If prolongation of QT or QT interval corrected for heart rate (QTc) is noted during the first 2 weeks, triplicate 12 lead ECGs will be conducted weekly during Cycle 2, and then once every 3 weeks before administration and 5-15 minutes after administration on Day 1 of every cycle from Cycle 3 onwards, until discontinuation of FN-1501 treatment. Refer to Section 7.1.3 for details on significant QTc prolongation.
7. Data obtained up to 42 days prior to Day 1 is acceptable.
8. Only in women of childbearing potential and additionally at the investigator's discretion.
9. In the event of neutropenia, thrombocytopenia, or ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequent as the investigator feels necessary until toxicity is resolved (≤ Grade 2). Refer to Table 6 for details on laboratory assessments.
10. Bone marrow biopsy for related assessments will be performed in patients with AML at Screening, every 6 weeks to coincide with the end of every other cycle, and at the end of the study or at time of relapse. Based on the patient's clinical condition, complete blood counts or bone marrow assessments may occur more frequently based on Investigator's judgment.
11. If urine protein is ≥ 2+ by dipstick, then 24-hour urine for total protein and a random urine for total protein and creatinine will be collected and evaluated. See Section 7.1.1 for details.
12. Refer to Table 3 for details. PK sample must be collected pre-dose on Day 3 of Cycle 1 and pre-dose on Day 1 of Cycle 2 and as detailed in Table 3.
13. The investigational drug should be administered at approximately same time each time. The investigational drug is administered on Days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. Not all treatment administration days are illustrated in the table.

Table 3: Sampling Schedule (Day 1 of Cycle 1 to Day 1 of Cycle 2 Only; Refer to Table 2 for complete schedule)

Cycle	**Cycle 1**											**Cycle 2**
Day of cycle	**Day 1**									**Day 2**	**Day 3**	**Day 1**
		Post-Day 1 Dose Time Point:										
Time point[1]	Pre-dose	5 min	15 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr	48 hr (pre-Day 3 dose)	Pre-dose
PK sample	X	X	X	X	X	X	X	X	X	X	X	X[1]	X[1]
ECG[2]	X				X	X							X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Abbreviations: ECG = electrocardiogram; hr = hour; min = minute; PK = Pharmacokinetic Time point relative to end of infusion on Cycle 1, Day 1. Blood sample will be collected pre-dose on Day 3 of Cycle 1 and Day 1 of Cycle 2. See next page for sampling time windows.
2. Vital signs and ECG also collected at follow-up not shown (see Table 2 for details). Vital signs and ECG are predose unless otherwise indicated.

Sampling Time Windows

The following time windows (relative to end of infusion) are allowed for PK sampling, ECG, and vital signs, as applicable:

- For pre-dose time points (Days 1, 3, and Cycle 2, Day 1): within 1 hr before dosing the planned study drug administration
- For 24 hr and 48 hr time points: +/- 1 hr., (prior to dosing on Day 3)
- For 2, 4, 6, 8 and 12 hr time points: +/- 30 min.
- For 30 min, 1 hr time points: +/- 15 min.
- For 15 min time point: +/- 5 min.
- For 5 min time point: +/- 3 min.

The actual time of PK sampling should always be recorded and entered in CRF.

4.1.4 Study Stopping Rules

The estimated duration of the study is contingent on the number of dose levels evaluated in the dose escalation. The study will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the study unjustifiable, or for administrative reasons by the Sponsor.

4.2 Selection of Study Population

4.2.1 Inclusion Criteria

Each patient must meet all the inclusion criteria for this study at the time of starting study treatment:

1. Male and female 18 years old and above
2. Able to understand and sign informed consent form
3. Patients with histologically or cytologically confirmed advanced solid tumors who have relapsed or refractory disease or relapsed/refractory AML for which no standard therapies expected to produce clinical benefit to the patient are available
4. Patients with diagnosed solid tumors must have at least one lesion that is measurable per RECIST v1.1 criteria
5. Patients with relapsed or refractory AML must be diagnosed with AML based on World Health Organization (WHO) criteria (≥ 20% blasts in bone marrow) Patients with acute promyelocytic leukemia are excluded.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
7. Have discontinued all previous cancer therapies for at least 21 days (for solid tumors) or at least 7 days (for AML) or 5 half-lives prior to study treatment, whichever is shorter, and recovered from the acute adverse effects of therapy
8. Expected to survive at least 2 to 3 months
9. Left ventricular ejection fraction (LVEF) ≥ 50% and QTc interval < 450 ms
10. Women shall meet either of the following conditions before enrollment
    - Infertile, defined as having a bilateral oophorectomy (ovariectomy), or a bilateral tubal ligation, or being post-menopausal for at least 1 year
    - For those of childbearing potential, they should have a negative serum pregnancy test during screening, agree to refrain from lactation, and use effective contraception such as hormonal methods associated with inhibition of ovulation, condom, intra-uterine device, surgical sterilization (including partner's vasectomy) or sexual abstinence during the study and 30 days after the last administration of study drug
11. Men who are engaging or plan to engage in sexual activity with a female of childbearing potential must either have a prior vasectomy or agree to use effective contraception such as condoms, sexual abstinence and appropriate methods taken by their partner(s) during the study and 90 days after the last dose

12. Patients must have adequate organ functions as indicated by the following screening laboratory values:
    - Serum total bilirubin ≤ 1.5 × ULN (Serum total bilirubin can be ≤ 3.0 × ULN if patients have hemolysis or congenital hemolytic diseases)
    - Creatinine < 1.5 × ULN or estimated creatinine clearance ≥ 50 mL/min
    - AST and ALT ≤ 2.5 × ULN (AST and ALT can be ≤ 5 × ULN for patient with liver metastases)
    - ANC ≥ 1.5 × 10^9/L
    - Platelets ≥ 100 × 10^9/L
    - Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L (Note: Criteria must be met without a transfusion within 2 weeks of obtaining the sample)

      Note: Laboratory requirements for complete blood counts (hemoglobin, ANC, and platelets) do not apply to AML patients

4.2.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not eligible to participate in this study:

1. Participation in another therapeutic clinical trial within 3 weeks of enrollment
2. A previous toxicity-related reaction to cancer therapy and have not recovered within 2 weeks of enrollment (>Grade 2 NCI-CTCAE Version 4.03)
3. Having received a major surgical operation within 4 weeks of enrollment or not completely recovered from a previous operation
4. Any serious or uncontrollable systemic disease, including but not limited to: Hypertension (after treatment, systolic blood pressure (SBP) > 180 mmHg and/or DBP > 100 mmHg) and active hemorrhagic disorders; patients who are determined by investigators as otherwise not suitable for participation in this study. Note: Patients that in the judgment of the investigator have clinical signs of disease progression during the screening period (i.e.: febrile neutropenia, ascites requiring drainage, hospitalization due to worsening underlying disease, etc.) will not be eligible for participation.
5. Active known infection, including hepatitis B, hepatitis C, and human immunodeficiency virus
6. Primary central nervous system (CNS) tumor or CNS metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth (patients with a history of CNS metastases or cord compression are allowable if they have been definitively treated and have been clinically stable for at least 3 months, and off steroids or anticonvulsants ≥ 2 weeks before first dose of study drug)
7. Serious kidney injury, requiring dialysis
8. Serious liver injury, and advanced liver diseases of Child-Pugh class B and C

9. On medications that are strong CYP3A inhibitors or inducers unless patients are willing and able to change to use of an equivalent medication that is not a strong CYP3A inhibitor or inducer
10. Cardiac function and disease history which meets one or more of the following conditions:
    - Any risk which may increase QTc interval prolongation, such as hypokalemia, hereditary long QT syndrome, and taking drugs that can prolong QT interval
    - Acute myocardial infarction ≤ 6 months prior to Day 1
    - Clinically significant arrhythmia ≤ 6 months prior to Day 1
    - Congestive heart failure ≥ Grade 3 by New York Heart Association (NYHA) ≤ 6 months prior to Day 1
    - Cerebral vascular accident (CVA) ≤ 6 months prior to Day 1
11. Are pregnant or breastfeeding

4.2.3 Patient Restriction

Patients should avoid grapefruit and products containing grapefruit.

4.2.4 Patient Completion and Discontinuation

4.2.4.1 Patient Completion

A patient will be considered complete if he/she has a valid PK profile and has not withdrawn from the study prior to completing the DLT assessment period (21 days from first dose of FN-1501).

4.2.4.2 Patient Discontinuation

A patient must be discontinued if any one or more of the conditions occur: 1) DLT occurs and the toxicity has not improved to Grade 1, Grade 0 or baseline within 14 days of onset; 2) occurrence of other toxicities that makes continuation of study treatment intolerable; 3) a third dose-reduction is required; 4) treatment delay is more than 4 weeks, unless resuming treatment is regarded beneficial to the patient by the investigator and agreed by Sponsor's medical monitor; 5) in the opinion of the investigator, continuous treatment is not beneficial to the patient.

A patient may voluntarily discontinue participation from this study at any time. If a patient is discontinued from participation in the study for any reason, the investigator must make every effort to perform the following evaluations 30 to 35 days from the last dose of FN-1501: physical examination, vital signs, ECG, laboratory tests (hematology, chemistry, coagulation, and urinalysis), and AE assessment. These data will be recorded as they comprise an essential evaluation that should be done prior to

discharging any patient from the study. If a patient is discontinued from the study at any time due to an AE (as defined in Section 9.1), the procedures stated in Section 9.7 must be followed.

The reason for discontinuation will be recorded in the electronic case report form (eCRF). These reasons may include:

- Withdrawal of consent by the patient
- Discontinuation of FN-1501 by the sponsor
- Pregnancy
- Any significant AE that compromises the patient's ability to participate in the study
- The investigator or sponsor determines it is in the best interest of the patient
- Progression of disease at any time during the study
- Need for prohibited medication
- Lack of compliance with the study and/or study procedures (e.g., administration instructions, study visits)
- Significant deviation from the protocol without the consent of the sponsor

Premature discontinuation of FN-1501 occurs when a patient is discontinued for reasons other than unacceptable toxicity during DLT evaluation cycle. Prematurely discontinued patients will be considered for replacement after due consideration from sponsor and SMC.

5 Study Treatments

5.1 Description of Study Drug

The product is a white to off-white sparse cake or powder contained in vials. Each vial contains 10 mg FN-1501. It will be reconstructed with 5% glucose prior to use.

5.2 Dosage and Administration

Patients will receive intravenous infusion of FN-1501 on the assigned days starting with the 2.5 mg/day cohort. FN-1501 will be diluted in 10 mL of 5% glucose solution and added in 100 mL 5% glucose for intravenous infusion over 1 hour. For procedures for dose escalation, refer to Section 4.1.1.

5.2.1 Dose Delays and Modifications

Interruption/reduction of dosing for AEs may take place any time during the study. Below are general guidelines for dose delays and modifications for FN-1501 related toxicities.

Dose Delays

Treatment with FN-1501 should be withheld from a patient who experiences an AE of Grade 3 or higher until the toxicity resolves to Grade 1, Grade 0 or baseline. Dosing with FN-1501 may be resumed following resolution of toxicity at the next lower dose level. The resumed dosing will be given at the next regularly scheduled time point. If the AE is clearly not associated with the study treatment, the dosing may be resumed at the original dose level, after discussion with the sponsor's medical monitor.

If a patient requires a treatment interruption of more than 4 weeks for any reason, the patient should be withdrawn from the study treatment, unless resuming the treatment is regarded beneficial to the patient by the investigator and agreed upon by the sponsor's medical monitor.

Dose Modifications

Dose reductions are allowed if patients resume study treatment after dose interruption for toxicity. A maximum of two dose reductions are permitted. If further dose reduction is needed, the patient should be withdrawn from study treatment.

A patient may switch to a higher dose at the discretion of the investigator, if 1) the safety of the higher dose level has been fully evaluated and determined not to exceed MTD; and 2) the patient has been treated at the current dose level for at least 2 cycles without experiencing a clinically significant treatment-emergent AE. However, if Grade 3 or higher toxicity occurs or continues after permitted dose increase or reduction, then the patient should be withdrawn from study treatment.

Any resumed or modified dose will start as a new cycle.

5.3 Precautions

Tumor Lysis Syndrome (TLS) has been reported as a potential risk in patients with AML, including those patients that have predisposing factors such as elevated lactate dehydrogenase, leukocytosis, tumor burden, hydration status and/or renal dysfunction.

Patients at risk of developing TLS or patients that develop TLS should be treated with prophylaxis and therapeutic measures respectively as per Institutional Guidelines.

5.4 Treatment Assignment

Patients will be identified by a subject number. Each patient enrolled in this study will receive a unique subject number, which will be assigned when the patient is screened or enrolled in the study. Each patient receiving FN-1501 will also receive a treatment allocation number. Subject numbers and treatment numbers will be assigned in chronological order starting with the lowest number. Once a subject number and treatment number have been assigned to a patient, it cannot be reassigned to another patient.

A patient who withdraws from the study for reasons other than DLT may be replaced. If a patient is replaced, the replacement patient will be assigned the next available subject number and treatment number.

5.5 Drug Preparation

Specific instructions for acquisition, storage and preparation of FN-1501 and preparation of final dosing solution will be provided in the Pharmacy binder provided to the sites.

5.6 Packaging and Labeling

The drug product is packed in 10 mL, type I glass vials. The vial is sealed with a bromobutyl stopper covered by an aluminum flip-off cap.

The contents of the label will be in accordance with all applicable regulatory requirements.

5.7 Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. Study drug must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug-specific requirements. The study drug must be stored as specified on the label and according to the latest version of the IB.

5.8 Product Accountability

The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug

accountability records throughout the course of the study. This person(s) will document the amount of study drug received from the sponsor, the amount supplied and/or administered to and returned by patients, if applicable. After completion of the study, all unused product will be inventoried and packaged for return shipment by the hospital unit pharmacist. The inventoried supplies will be returned to the sponsor or destroyed on site after receiving written sponsor approval.

5.9 Assessment of Compliance

Patients will receive FN-1501 by intravenous infusion at the investigational site as outlined in the Study Assessment and Procedure Schedule (Table 2). All visits and treatment administrations will be recorded.

6 Concomitant Medications and Nondrug Therapies

6.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration according to the Study Assessment and Procedure Schedule (Table 2). All prescription or non-prescription (over the counter) medications, as well as, vitamins, herbs and supplements taken, any special diets and alcohol use should be collected.

6.2 Prohibited Medications

Administration of all other anti-cancer therapy (cytotoxic, biologic, radiotherapy, or hormone therapy other than for replacement) while on treatment in this study is prohibited. Palliative radiotherapy for non-targeted lesions is permitted. Bisphosphonate use is permitted if the patient has already been on it for three or more months and on a stable dose. Corticosteroid courses of limited duration (2 weeks or less) are permitted, if used to treat a concomitant (non-cancer) medical condition.

During study treatment, drugs known to prolong the QT/QTc interval should be avoided unless there is no alternative treatment available, in accordance with ICH E14 [9]. If such a drug must be used, written approval from the sponsor's medical monitor is required. A list of drugs with QTc prolongation potential is presented in Table 4. A full list is provided through the Arizona Center for Education and Research on Therapeutics (CERT; "Drugs That Prolong the QT interval and/or Induce Torsades de Pointes"): Available at:
https://crediblemeds.org/index.php/tools/pdfdownload?f=cql_en

Table 4: Drugs with QTc prolongation potential

Antipsychotics	**Type IA antiarrhythmics**	**Type IC antiarrhythmics**	**Class III antiarrhythmics**
Chlorpromazine	Quinidine	Flecainide	Sotalol
Haloperidol	Procainamide	Encainide	Amiodarone
Droperidol	Disopyramide		
Quetiapine			
Olanzapine			
Amisulpride			
Thioridazine			
Tricyclic antidepressants	**Other antidepressants**	**Antihistamines**	**Other**
Amitriptyline	Mianserin	Diphenhydramine	Chloroquine
Doxepin	Citalopram	Astemizole	Hydroxychloroquine
Imipramine	Escitalopram	Loratidine	Quinine
Nortriptyline	Venlafaxine	Terfanadine	Macrolides
Desipramine	Bupropion		Erythromycin
	Moclobemide		Clarithromycin

While the primary metabolic pathway for FN-1501 involves the CYP3A isoform, preliminary in vitro screening assays revealed that FN-1501 is not a strong inhibitor nor a strong inducer of human CYP isoenzymes tested. The use of drugs that are strong CYP3A4 inhibitors or inducers is prohibited (Table 5). Patients who require moderate CYP3A4 inhibitors during the study should be closely monitored. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a complete list of CYP3A inhibitors.

Table 5: Prohibited Medications

Strong CYP3A inhibitors			
Indinavir	telithromycin	suboxone	nelfinavir
Itraconazole	ketoconazole	ritonavir	saquinavir
nefazodone	clarithromycin		
Strong CYP3A inducers			
Carbamazepine	rifampicin	phenobarbital	phenytoin
St. John's wort			

Abbreviations: CYP = cytochrome P450

6.3 Other Medications to be Used with Caution

Gene expression data showed that FN-1501 is an inducer of CYP1A2 at the concentration of 0.100 μM. FN-1501 also showed weak inhibition on CYP2C8 (IC_{50}: 38.8 μM). Investigators should be aware that FN-1501 has the potential to interfere with the appropriate metabolism of medications that rely on these isoenzymes. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for the medication list.

7 Safety, Pharmacokinetic, Pharmacodynamic, and Other Assessments

A signed, written informed consent must be obtained prior to screening assessments and before any study-specific assessments are initiated. The study-specific assessments and procedures are shown in Table 2. The PK sampling, vital sign and ECG time points are presented in Table 2 and Table 3. Demographic and Baseline Assessments will include date of birth, race, height (in cm), body weight (in kg), and body mass index (BMI [in kg/m^2]). For height and weight measurements, the patient will be allowed to wear indoor daytime clothing with no shoes. This data will be captured in the eCRF and database. After giving consent, patients will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the criteria listed in Section 4.2. Screening assessments will be completed within 21 days prior to the first dose of the study drug, except that radiological scans of tumor can be within 42 days prior to the first dose (Section 7.4).

Screening assessments completed within 72 hours of administration can be used as Day 1 of Cycle 1 assessments as indicated in Table 2. The screening assessments will include:

- Demographic data
- Medical history & baseline conditions
- Vital signs (SBP, DBP, pulse rate, temperature, and respiratory rate)
- Height and weight (BMI calculation)
- Complete physical exam
- ECOG performance status
- 12-lead ECG
- Review of concurrent medications
- CT or MRI
- Disease assessment for Solid Tumors or AML
- Pregnancy test for women of childbearing potential

- Hematology
- Blood chemistry plus serum amylase and lipase tests
- Bone marrow biopsy for related assessments for patients with AML (see Section 7.4)
- Coagulation test
- Urinalysis
- Recording of AEs and SAEs

The above-mentioned data will be captured in the source documents and entered into the eCRF. All tests will be done by local laboratories. Any results falling outside the normal range will be repeated at the discretion of the investigator.

7.1 Assessments During the Treatment Period

Routine safety assessments include vital signs, weight, physical exam, and AE assessment will be performed at every visit. Other safety assessments include 12-lead ECG, bloodwork, disease assessments, bone marrow biopsy for related assessments for patients with AML, and urinalysis will be performed as indicated in Table 2.

7.1.1 Local Laboratory Evaluation

Laboratory assessments will be performed at a local certified laboratory at the time points specified in Table 2. Laboratory assessments need not be repeated on Day 1 if these assessments were completed for screening within 72 hours prior to the first administration. Required laboratory assessments are listed in Table 6.

Table 6: Clinical laboratory assessments

Blood Chemistry	Hematology	Coagulation	Urinalysis (dipstick)
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Bicarbonate Electrolytes (Ca, K, Na, Cl, P) Creatinine Glucose Lactate dehydrogenase Magnesium Phosphorus Serum amylase* Serum lipase* Total protein Total bilirubin Urea	Full and differential blood count Red blood cell count Hematocrit Hemoglobin Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet counts White blood cell count with differential Neutrophil count	Prothrombin time Partial thromboplastin time	Appearance pH Specific gravity Glucose Protein Ketones Blood cells

Abbreviations: Ca = calcium; Cl = chloride; K = potassium; Na = sodium

* These tests will be conducted together with blood chemistry.

Laboratory results should be assessed by the Investigator. In the event of neutropenia (ANC <1000/mm^3), thrombocytopenia (platelets <50,000/mm^3), or Grade 3 clinical chemistry toxicity, the relevant assessments will be conducted as frequently as the Principal Investigator feels is needed until toxicity resolves to ≤ Grade 2. If warranted, additional testing can also be done, or the relevant tests done more frequently in accordance with institutional guidelines. All patients who have any Grade 3 or Grade 4 laboratory abnormalities at withdrawal from the study must be followed up until they have returned to Grade 1 or Grade 2, unless these are not likely

to improve due to the underlying disease. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then 24-hour urine for total protein and a random urine sample for total protein and creatinine will be obtained. If urine protein is > 2 g/24 hours, study drug administration will be interrupted until it returns to ≤ 2 g/24 hours. If urine protein is ≤ 2 g/24 hours, further clinical evaluation and/or more frequent testing may be performed as clinically indicated. A random urine protein to creatinine ratio can serve as a reliable surrogate for the 24-hour urine protein when following patients with urine protein of ≤ 2 g, documented by a 24-hour urine collection. In such cases, the 24-hour urine for total protein should be repeated only if a clinically significant increase is observed in the random urine protein to creatinine ratio. After week 9, this test will be performed as clinically indicated.

7.1.2 Physical Examination and Vital Signs

A complete or targeted physical examination, vital signs (SBP, DBP, pulse rate, temperature, and respiratory rate), and weight examination will be performed at the time points specified in Table 2.

Complete physical examination includes assessments of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes/spleen, skin, oropharynx and extremities. Targeted physical examinations should be limited to systems of clinical relevance (i.e., cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms.

7.1.3 Electrocardiogram

A 12-lead ECG will be performed in triplicate at Screening, on Cycle 1, Day 1, Cycle 2, Day 1. Thereafter, triplicate is only if clinically indicated (i.e., prolonged QTc interval) as detailed in Table 2. ECGs will be performed on the days specified in Table 2 and time points specified in Table 3. Other ECGs may be performed as clinically indicated. Patients should be in the supine position for at least 10 minutes prior to having ECGs performed and remain in that position for the duration of the test.

Patients with significant QTc prolongation to undergo 12-lead ECG as detailed in Table 2. Significant QTc prolongation will be defined as an interval > 500 msec; an interval which increases by ≥ 60 msec over baseline, and/or decreased by 50 msec below pre-dose recording. The ECG tracing should be examined and interpreted by a trained physician.

If prolongation of QT or QT interval corrected for heart rate (QTc) is noted during the first 2 weeks, triplicate 12 lead ECGs will be conducted weekly during Cycle 2, and then once every 3 weeks before administration and 5-15 minutes after administration

on Day 1 of every cycle from Cycle 3 onwards, until discontinuation of FN-1501 treatment.

If a patient has significant QTc prolongation:

- He/she will suspend study drug administration
- The patient will be medically assessed, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 msec of baseline
- The medical monitor will be consulted prior to administering further doses or re-challenging
- The medical monitor will be consulted prior to administering higher doses

7.1.4 Computed Tomography

CT scan with contrast will be performed to assess all known diseases in patients with solid tumors. CT scans must encompass neck, chest, abdomen, and pelvis and include oral or intravenous contrast. MRI may be used in place of CT in clinical scenarios where anatomical location of an evaluable lesion (such as soft tissue) precludes accurate measurement by CT. The CT scan will be used for disease assessment by the investigator at each study center. For patients who discontinue early, a CT scan will be performed at the end of study visit if the previous scan was more than 3 months ago. Note: CT scans do not apply to patients with AML.

7.1.5 Adverse Events

All AEs and SAEs, regardless of the relationship to the study drug, will be collected from consenting patients, starting from signed informed consent form until 30 days after their last dose of FN-1501, or until resolution of all study drug related AEs, whichever is longer.

7.2 Safety

Measurements used to evaluate safety will include vital signs, clinical laboratory tests, 12-lead ECG, and physical examinations. Throughout the study, the study center personnel will be monitoring AEs. AEs and toxicities will be graded according to NCI CTCAE, Version 4.03.

7.2.1 Pregnancy

7.2.2.1 Pregnancy Testing

A serum pregnancy test will be performed at screening and a urine pregnancy test at the time points specified in Table 2 in women of childbearing potential. Any female patient who is pregnant will not be eligible for the study.

The results of pregnancy tests will be recorded in the database.

7.2.2.2 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is from screening to the 30-day post-study follow-up/end of study visit. Information on pregnancies identified prior to the study drug administration does not need to be reported to the sponsor.

7.2.2.3 Action to be Taken if a Pregnancy Occurs

A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study. All post-study assessments will be collected at the time of discontinuation. The investigator, or his/her designee, will collect pregnancy information on any female patient or a female partner of a male patient who becomes pregnant while participating in this study.

The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE, as described in Section 9.6 and will be followed as described in Section 9.8.

A spontaneous abortion is always considered to be an SAE and will be reported. Furthermore, any SAE occurring because of a post-study pregnancy and which is considered reasonably related to the study drug by the investigator, will be reported to the sponsor as described in Section 9.8. While the investigator is not obligated to actively seek this information in former patients, he/she may learn of an SAE through spontaneous reporting.

7.3 Safety Follow-up Assessment

Approximately 30 days after the last administration of the study drug, all patients should return for a final evaluation. Assessments to be performed are presented in Table 2.

Any abnormal finding of clinical consequence and not related to the disease progression will be monitored until resolution or baseline status.

7.4 Efficacy

Efficacy is not a primary objective of this study. Anti-tumor activities will be evaluated in solid tumors by treating investigators according to RECIST version 1.1, performance status, CT/MRI image and tumor marker (if applicable) at designated time points and time of event (Table 2). CR, PR, SD, PFS, and duration of response will be summarized.

In patients with AML, response will be evaluated according to the AML response criteria at designated time points and time of event (Table 2) [5]. Bone marrow biopsy for related assessments will be performed in patients with AML at the end of every other cycle, at the end of the study or at time of relapse. Based on the patient's clinical condition, complete blood counts or bone marrow assessments may occur more frequently based on investigator's judgment.

In patients with AML only:

Bone marrow biopsy for related assessments:

- Bone marrow cellularity
- Total Cells Counted
- Blasts in Marrow
- Classical Cytogenetic Analysis

7.5 Pharmacokinetics

Blood samples will be collected to determine the plasma concentration and describe the PK profile of FN-1501 and for a preliminary analysis of major metabolites.

The maximum total amount of blood taken for the PK analysis will be approximately 4 mL. These samples will be collected at the time points presented in Table 3. Should a patient undergo an intra-patient dose escalation, additional PK samples may be collected (in addition to those listed in Table 3) following the same schedule in Table 3. Frozen plasma samples should be shipped as soon as possible after collection since exposure will be monitored while the study is ongoing.

Cannulation for blood sampling for PK will be performed. Blood will be collected via the intravenous cannula pre-dose and at the time points specified in Table 3. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Study Manual. Blood samples (4 mL) for

PK analysis will be collected into plastic collection tubes with potassium ethylenediaminetetra acetic acid. Blood samples will be immediately chilled on crushed ice. Plasma will be separated by centrifugation (at approximately 1,000 × g for 10 to 15 minutes at 4°C) and will be transferred to labeled polypropylene storage tubes. Samples will be immediately frozen in an upright position to keep the plasma in the bottom of the tube. Samples must remain frozen in a freezer set at or below -70°C and in a box with dry ice during shipping.

Prior to sample collection, the collection tube and plasma storage tube must be labeled with the corresponding labels provided by the sponsor. The labels must be placed along the length of the tube so they can be read easily. Tape must not be used to secure the labels as the tube will not fit into the auto-analyzer test tube rack. The labels are of high quality and will not peel off the tube even under extreme conditions.

Should a drug-drug interaction (DDI) between FN-1501 and a concomitant medication be suspected, further blood samples for PK analyses may be collected to characterize the extent of the interaction.

Samples will be shipped to the central laboratory where all samples will be analyzed for plasma concentrations of FN-1501 and M3 using a validated method.

7.6 Appropriateness of Measurements

All safety, efficacy and PK assessments used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant.

8 Quality Control and Quality Assurance

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs). Quality control will be applied to each stage of data handling. The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Certified local laboratories for laboratory measurements and ECGs
- Study center initiation visit
- Early study center visits post-enrollment
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning

- Internal review of data
- Quality control check of the final clinical study report

In addition, the sponsor and/or the Clinical Research Organization (CRO) clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, central laboratories, vendors, clinical database, and the final clinical study report. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

8.1 Monitoring

In accordance with applicable regulations, Good Clinical Practice (GCP), and the sponsor's procedures, the sponsor and/or CRO monitors will contact the study center prior to the patient enrollment to review the protocol and data collection procedures with study center personnel. In addition, the monitor will periodically contact the study center, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution

This will be done to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.1.

8.2 Protocol Amendment and Protocol Deviation

Amendments to the protocol that entail corrections of typographical errors, clarifications, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for information only. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

The sponsor must be informed of any protocol deviations and/or violations. The deviation/violation and the reasons will be included in the clinical study report. The investigator is responsible for reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority.

8.3 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of CRO.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated.

The eCRFs should always reflect the latest observations of the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data once complete.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data has been entered in the eCRF, any corrections or alterations to the data fields will be traceable via an audit trail, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for

entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will respond to any queries raised.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each patient who receives the study drug, regardless of the duration. Patients will be given a subject identification number to maintain anonymity. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject identification number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 or higher. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 17.0 or higher.

8.4 Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all

relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

9 Adverse Event and Serious Adverse Event

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol. AE and SAE collection are to begin at the time of patient consent and continue until 30 days after last dose of FN-1501, or until resolution of all study drug-related AEs.

9.1 Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, is considered AE. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug. Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication.
- Significant failure of expected pharmacological or biological action. See Section 9.3 for additional information.

Examples of an AE do not include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

9.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurs or is necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

- Results in disability/incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, vital signs, etc.) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or an SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.4 Time Period, Frequency, and Method of Detecting Adverse Events and Serious Adverse Events

Patients will be assessed for AEs and SAEs beginning from the time of patient consent, and continue until 30 days after last dose of FN-1501, or until resolution of all study drug related AEs.

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs will be reported in the eCRF.

9.5 Recording of Adverse Events and Serious Adverse Events

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor in lieu of completion of the appropriate AE or SAE eCRF pages. However, there may be instances when copies of medical records for certain cases are requested by the Safety Specialist In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be

documented as the AE or SAE and not the individual signs/symptoms. AEs are independent components of the study.

9.6 Evaluating Adverse Events and Serious Adverse Events

9.6.1 Assessment of Intensity

The investigator will assess the intensity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI CTCAE Version 4.03.

9.6.2 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The investigator will also consult the IB and/or Product Information for marketed products in determining his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses the causality for every event prior to transmission of the SAE eCRF to the sponsor. The investigator may change his/her opinion of causality in light of follow-up information, and may amend the SAE eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality as per instructions on the SAE eCRF. The categories of causality assessment are: Not Related, Possibly Related, and Probably Related.

9.7 Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and which are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include

additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If the patient dies during the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE eCRF, with all changes signed and dated by the investigator. The updated SAE eCRF should be resent to the sponsor within the time frames outlined in Section 9.8.

9.8 Prompt Reporting of Serious Adverse Events

9.8.1 Timeframes for Submitting Serious Adverse Events

SAEs will be reported promptly in the eCRF as described in Table 7 once the investigator determines that the event meets the protocol definition of a SAE.

Table 7: Timeframe for Reporting Serious Adverse Events to the Sponsor

Type of SAE*	**Initial SAE report**	**Document**	**Follow-up SAE report**	**Document**
Timeframe	24 hours of investigator's knowledge	SAE form (eCRF)	ASAP	SAE form (eCRF) Update

Abbreviations: ASAP = As soon as possible eCRF = electronic case report form; SAE = serious adverse event

*Pregnancy will be reported as SAE and follow the same timeframe.

9.8.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information into the eCRF within 24 hours as outlined in Section 9.8.1. The SAE form in the eCRF should be completed as thoroughly as possible with all available details of the event, and the sponsor should be informed within the designated timeframes. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.6.2.

All SAEs should be reported through eCRF. In rare circumstances that eCRF cannot be accessed temporarily, paper SAE form should be submitted to meet the timeline and the site must enter the information from the paper SAE form into eCRF as soon as the eCRF becomes available. In the absence of facsimile equipment, notification by telephone is acceptable, which must be followed by an overnight email addressed to Clinipace Safety Group attaching a copy of the SAE form Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE form within the time frames outlined in Section 9.8.1.

Safety Group contact information is available in the Protocol Contact List available in the investigator's study file.

The following pages of the eCRF must accompany the SAE forms: "demography", "medical history", "concomitant medications", "study medication records", and "death form" (if applicable).

9.9 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.8.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/ IEC.

This protocol is being filed under an Investigational New Drug (IND) application with the US FDA. Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators filed to the IND (or to associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. Such a report is prepared for an SAE that is both attributable to study drug and unexpected. The purpose of the report is to

fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (e.g., revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.10 Post-study Adverse Events and Serious Adverse Events

A post-study AE or SAE is defined as any event that occurs outside of the AE/SAE detection period.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably related to the study drug, the investigator will promptly notify the sponsor.

9.11 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests), even if it occurs during the post-treatment period, will be reported promptly to the sponsor.

10 Data Analysis and Statistical Considerations

10.1 Sample Size Consideration

The number of dose levels examined and the emerging FN-1501 toxicities will determine the sample size. Based on toxicity data, 7 cohorts may be required to establish the dose of FN-1501 for phase 2 study. Assuming DLT starts to occur at the dose of 12.5 mg/day (4^{th} cohort) and therefore, 6 patients will be enrolled into this and subsequent cohorts, it is estimated that approximately 33 patients will be required to establish the RP2D(s) of FN-1501.

The number of patients in each cohort has been based on a standard 3+3 with the desire to obtain adequate tolerability, safety, and PK data while exposing as few patients as possible to the study drug and procedures.

10.2 General Consideration for Data Analysis

Data will be listed and summarized according to reporting standards chosen by the sponsor. Refer to the statistical analysis plan for details.

10.2.1 Analysis Populations

All patients who are exposed to FN-1501 will be included in the safety population. All patients who have at least one measurable concentration and for whom valid PK parameters can be estimated will be included in the PK population.

10.2.2 Interim Analysis

No interim analysis is planned for this study. Since this is a dose escalation study, safety, PK, and PD data will be evaluated on an ongoing basis.

10.2.3 Withdrawal

Patients who are withdrawn prior to the completion of the DLT assessment period for reasons other than DLT will be replaced whenever possible.

10.3 Safety Analysis

All patients who are exposed to FN-1501 will be evaluated for safety.

AE rates and changes in laboratory results by dose levels will be summarized in tabular form. AEs representing clear evidence of disease progression will not be considered relevant to the assessment of toxicity.

AEs and toxicities will be graded according to NCI CTCAE, Version 4.03 or higher.

AEs of special interest will be defined in the statistical analysis plan. SAEs, treatment related AEs and AEs leading to treatment discontinuation will be summarized overall. Hematology, clinical chemistry, coagulation and urinalysis values will be listed for each patient and flagged as high or low relative to the normal range, where applicable. Pre-dose values will be used to assess laboratory shifts occurring post-dose. A comparison of pre-study and post-study values will be performed to identify any parameters that have not returned to pre-study levels.

AEs will be coded and grouped using the MedDRA Version 17.0 or higher. All AEs will be listed.

All ECG parameters including the QT interval corrected for heart rate (QTc) will be listed for each patient and summarized by dose level and assessment time. Change from baseline will also be summarized. Relationship between dose level and QTc changes will be explored by graphs. Additional exposure-response analysis may be conducted to evaluate QT/QTc prolongation. QTc will be calculated using both Fridericia's and Bazett's formulae.

10.4 Pharmacokinetic Analyses

PK analyses will be conducted on patients who have received at least 1 dose of the study drug and have had sufficient post dose samples collected to allow estimation of PK parameters. PK data before the first dose at Day 1 of Cycle 1, and after the first dose at Day 1 of Cycle 1 (multiple time-points), Day 3 of Cycle 1, and Day 1 of Cycle 2 will be analyzed. PK parameters will be derived using appropriate software.

Plasma samples will be collected according to the time points listed in Table 3. Where possible, the following plasma PK parameters will be determined for FN-1501 and major metabolites: $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, $t_{1/2}$, V_d, CL, and LI.

Plasma concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard non-compartmental and/or compartmental PK methods. The PK parameters for a single dose profile (AUC, C_{max}, t_{max}, $t_{1/2}$, CL, and V_d) will be calculated, if there are sufficient data. Individual patient parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, and the standard deviation and geometric mean of log-transformed parameters) by treatment group will be reported. Individual patient parameter values will be plotted against dose.

Population PK data may be pooled with data from other studies to investigate any association between drug exposure and biomarkers or significant safety endpoints. Alternative dosing approach, e.g., body size-based or fixed dosing, may be evaluated using a population approach. The results of these analyses, if performed, may be reported separately.

Dose proportionality of AUC and C_{max} for FN-1501 will be assessed using the power model as described below and evaluated visually in graphical form:

A linear regression model with the logarithm of the PK parameter (AUC, C_{max}) as the dependent variable and the logarithm of the dose as the independent variable ($\log[PK]=\alpha+\beta*\log[Dose]$) will be fitted. The model parameters (slope [β] and intercept [α]) will be estimated using least square regression. A minimum of 3 values per dose must be available for a given PK parameter to estimate dose proportionality with the power model. Point estimates and corresponding 2-sided 95% confidence intervals for the slope parameter and the intercept parameter will be provided.

10.5 Efficacy Analyses

Tumour response data will be listed and summarised by dose level using the following response categories: CR, PR, SD, progressive disease and not evaluable (NE) in solid tumors. Morphologic leukemia-free state in patients with AML.

11 Ethics

11.1 Regulatory Authority Approval

The sponsor will submit the protocol and where necessary obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

11.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential patients (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new patients consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.3 Informed Consent

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.4 Investigator Safety Reporting Requirements

The investigator or CRO is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

12 Study Administration

12.1 Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

12.2 Records Retention

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional

policy, some of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the study center, transfer of ownership of the study site.

12.3 Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator. In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patients.

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

12.4 Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.
- Information which is necessary to disclose to provide appropriate medical care to a patient.
- Study results which may be published as described in Section 12.4.1.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.4.1 Publication Policy

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the study center (collectively, a "Publication"), the investigator shall provide the sponsor with a copy of the proposed Publication and allow the sponsor a period of at least 30 days (or, for abstracts, at least 5 working days) to review the proposed Publication. Proposed Publications shall not include any sponsor information other than the study results or any personal data on any patient, such as name or initials.

At the sponsor's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow the sponsor to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

13 References

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14 Appendices

Appendix 1: SIGNATURE OF INVESTIGATOR

Protocol Title	A phase 1, multi-center, open-label, single-arm, dose-escalation, clinical study to evaluate the safety, tolerability, pharmacokinetics (PK) and anti-tumor activity of FN-1501 monotherapy in patients with advanced solid tumors or relapsed/refractory Acute Myeloid Leukemia (AML)
Protocol No.	FN-1501-UP1

This protocol is a confidential document of Shanghai Fosun Pharmaceutical Development Co., Ltd.

I confirm that I have read and understood this protocol, and will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (CGP) and the applicable laws and regulations. Upon acceptance of this document I agree that no unpublished information contained herein will be published or disclosed without prior written approval from Shanghai Fosun Pharmaceutical Development Co., Ltd.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____ _____

Investigator Title: _____ ____

Name/Address of Center: _____ ____