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CLINICAL STUDY PROTOCOL

Protocol Number:	**FF1050101US101**
Protocol Title:	A Phase 1/2a, dose-escalation study of FF-10501-01 for the treatment of advanced hematologic malignancies
Study Chair:	**Guillermo Garcia-Manero, MD** Professor of Medicine Chief, Section of Myelodysplastic Syndromes Deputy Chair, Translational Research Department of Leukemia The University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd. Unit 428 Houston, TX 77030-4009 Telephone: (713) 745-3428
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Original Protocol	**February 24, 2014**
Amendment 1	**April 17, 2014**
Amendment 2	**September 22, 2014 (revised October 8, 2014)**
Amendment 3	**November 23, 2015**
Amendment 4	**July 26, 2016**
Amendment 5	**February 7, 2017**
Amendment 6	**July 14, 2017**
Amendment 7	**Oct 12, 2017**

INVESTIGATOR SIGNATURE PAGE

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of ICH Good Clinical Practice, the Declaration of Helsinki and the applicable U.S. Food and Drug Administration (FDA) regulations.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the Institutional Review Board (IRB) or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document (ICD) used will have the approval of the IRB.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete and submit the electronic case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of FUJIFILM Pharmaceuticals U.S.A., Inc. (FPHU), Westat, the IRB or local regulatory authorities. I will ensure that I and my staff are available to meet with representatives of FPHU and Westat during regularly scheduled monitoring visits.

I will notify the Medical Monitor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to FPHU/Westat as soon as possible, but no later than 5 days following the initial notification.

Principal Investigator's Signature	**Date**
Principal Investigator's Name (Print)	

SYNOPSIS

Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.	**Protocol Number:** FF1050101US101
Name of Study Drugs (reagents): FF-10501-01	**Protocol Title:** A Phase 1/2a Dose-escalation Study of FF-10501-01 for the Treatment of Advanced Hematologic Malignancies
Name of Active Ingredient: 4-carbamoylimidazolium-5-olate	**Phase of Development:** Phase 1/2a

Primary Objective:

- To determine the safety and tolerability in subjects who receive FF-10501-01 for the treatment of advanced hematologic malignancies

Secondary Objectives:

- To determine the overall response rates
- To evaluate the proportion of subjects who achieve hematologic improvement in peripheral blood or bone marrow blast count
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To evaluate the pharmacokinetics of FF-10501 and M1
- To evaluate xanthosine monophosphate (XMP) as a pharmacodynamic marker

Methodology:

This is a Phase 1/2a, dose-escalation study of FF-10501-01 for the treatment of advanced hematologic malignancies.

A total of up to N= 68 subjects will be enrolled in the study. Subjects with acute myelogenous leukemia (AML) (Phase 1 only), myelodysplastic syndrome (MDS), and chronic myelomonocytic leukemia (CMML) will be included.

Major selection criteria are: age ≥ 18 years, confirmed MDS/CMML or AML (Phase 1 only for AML) with documented disease progression following previous therapy, or subjects with AML ≥ 60 years of age who are not candidates for other therapies (Phase 1 only). Subjects must be ≥ 3 weeks beyond chemotherapy, radiotherapy, major surgery, or other experimental treatments, and recovered from all acute toxicities (≤ Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1:

14-day Schedule: Following Screening, a total of 6 cohorts of 3 subjects each received oral doses of 50, 100, 200, 300, 400 or 500 mg/m^2 BID per day (100, 200, 400, 600, 800 or 1000 mg/m^2/day) for 14 days, followed by 14 days off, repeated every 28 days (= 1 cycle). Three events of drug-related atrial fibrillation (Grade 2) were reported in 2 subjects at a dose of 500 mg/m^2 BID (Cohort 6). Study drug was suspended in both subjects and all events resolved with oral metoprolol treatment. These events were medically important events and thus met the definition of dose-limiting toxicity (DLT). No further enrollment was made at this dose level. The maximally tolerated dose (MTD) was declared at 1 dose level below the dose eliciting DLT, 400 mg/m^2 BID, and this

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Methodology continued:

cohort was expanded to 6 subjects. No DLTs have been observed in N=7 total subjects treated at 400 mg/m^2 BID x 14 days.

21-day Schedule: At the MTD of 400 mg/m^2 BID, Cohort 7 was added to extend the BID dosing schedule to 21 days followed by 7 days off, repeated every 28 days (=1 cycle) (Amendment 3).

28-day Schedule: At the MTD of 400 mg/m^2 BID, Cohort 8 was added to extend the BID dosing schedule to 28 days continuous dosing each 28 days (=1 cycle) (Amendment 4).

DLT is defined as Grade 4 hematologic toxicity lasting 7 days or more; Grade 3 nonhematologic toxicity of any duration not amenable to supportive care; failure of platelets, absolute neutrophil count (ANC), or hemoglobin (Hb) to recover to Grade 1 within 12 weeks despite use of platelet and red blood cell (RBC) transfusions and/or growth factors; febrile neutropenia (defined as ANC<1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour); Grade 3 thrombocytopenia associated with bleeding; or other important medical event.

For all subject cohorts, if 1 of 3 subjects per cohort experiences DLT, the cohort will be expanded to 6. If 2 of 6 subjects per cohort experience DLT, all further dose escalation will stop. If 0 of 3 or ≤ 1 of 6 subjects per cohort experience DLT by Day 28 following dosing of FF-10501-01, dose escalation will proceed to the next cohort. At the MTD of 400 mg/m^2 BID, the longest schedule of administration below the schedule of administration eliciting DLT will be declared the recommended Phase 2 dose (RP2D) and schedule. A total of 6 subjects will be treated at the RP2D and schedule. No intra-subject dose escalation will be allowed from previous dose levels/schedules of administration until at least one subject has completed Cycle 1 at the longer schedule of administration (e.g., 21 or 28 days) with no Grade 2 or greater toxicities observed. Additionally, patients currently on study will have the option to extend their current dosing schedule to 21 days, followed by 7 days off, repeated every 28 days (=1 cycle), or 28 days of continuous dosing, whichever is chosen as the best schedule, if seen in the patient's best interest by the principal investigator. Dose level adjustments for DLT will be made. Subjects who experience DLT at the first dose level, 50 mg/m^2 BID, will not be dose-reduced. Up to 48 subjects are planned for Phase 1.

Phase 2a: Once 6 subjects are treated at the RP2D and schedule in Phase 1, 1 additional cohort will enroll 20 subjects with MDS/CMML who have relapsed from, or are refractory to, prior hypomethylating agent (HMA) therapy. Subjects enrolled in Phase 1 at the RP2D and schedule and who meet the Phase 2a selection criteria will count towards the Phase 2a accrual. Dose level adjustments for adverse events will be made.

During the study, a Safety Review Committee, consisting of the actively recruiting investigators, the Medical Monitor, and FPHU, will review data from each cohort on an ongoing basis.

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Methodology continued:

Subjects on the 21-day schedule will receive FF-10501-01 on a BID schedule. For all subjects on the 21-day dosing schedules, blood samples for pharmacokinetic assessment of FF-10501 and M1 in plasma will be collected on Cycle 1 Day 1 pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose, and Day 15 pre-dose (within 15 minutes prior to dosing), between 0.5-1 hr post-dose, and between 2-4 hr post-dose.

Blood concentration of xanthosine monophosphate (XMP) will be assessed as a pharmacodynamic endpoint.

For subjects on the 21-day dosing schedules, blood samples for XMP assessment will be collected on Cycle 1 Day 1 pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose, and Day 15 pre-dose (within 15 minutes prior to dosing), between 0.5-1 hr post-dose, and between 2-4 hr post-dose.

Disease assessments, including analysis of blood and bone marrow aspirates, will be performed at the end of Cycle 1 and Cycle 3 and every 2 cycles thereafter. Disease assessments may be performed at other time points at the discretion of the investigator.

Subjects who demonstrate objective response (OR) or stable disease (SD) will be allowed to continue therapy with FF-10501-01 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the subject's condition that prevents further study participation.

Blood for hematology, platelet and serum chemistry determinations will be collected within 28 days of Cycle 1 Day 1, on Days 1, 8, 15 and 22 of Cycle 1, on Day 1 of each subsequent cycle and at the End of Study Visit. Urine will be collected for urinalysis within 28 days of Cycle 1 Day 1, on Day 1 of each subsequent cycle and at the End of Study Visit.

Number of Subjects and Centers: Phase 1: Up to 48 subjects are planned for the dose-escalation phase. Phase 2a: A total of 20 subjects with MDS/CMML treated at the RP2D are planned, including MDS/CMML subjects treated at the RP2D in Phase 1. Therefore, up to 68 total subjects are planned.

The study will be conducted at up to seven sites.

Duration of Study: The accrual phase for the Phase 1 dose escalation phase is expected to be 12 – 18 months. The expected accrual for the Phase 2a expansion phase is expected to be 6 – 12 months, with the last subject followed up to 6 months, for a total study duration of 30 – 36 months. The anticipated accrual rate for the Phase 2a portion is 4 – 5 subjects per month.

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Inclusion Criteria:

- Males and females ≥ 18 years of age
- Subjects with confirmed advanced hematologic malignancies:
  - Phase 1:
    - High-risk MDS/CMML (defined as ≥ 10% peripheral blood or marrow blasts and/or International Prognostic Scoring System [IPSS] score ≥ 1.5) and relapsed or refractory to prior therapy
    - AML relapsed or refractory to prior therapy, or ≥ 60 years of age and not a candidate for other therapies
  - Phase 2a:
    - MDS/CMML, relapsed from, or refractory to, prior HMA therapy; the latter defined as failure to achieve clinical remission (CR), partial remission (PR) or hematologic improvement (HI) after previous HMA therapy (≥ 4 cycles of azacitidine or decitabine), or progression during, or toxicity to, previous HMA therapy precluding further HMA treatment, and
    - Bone marrow blast count ≥ 10% or peripheral blast count ≥ 5%, or IPSS-R score ≥ 3.5
- At least 3 weeks beyond the last chemotherapy, targeted anticancer agent, major surgery or experimental treatment and recovered from all acute toxicities (≤ Grade 1). *Hydroxyurea used to control peripheral blast counts is permitted up to Day 7 of treatment on study.*
- Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2
- Adequate renal and hepatic function:
  - Creatinine ≤ 2.0 mg/dL, or calculated creatinine clearance ≥ 45 mL/minute per the Cockcroft-Gault formula
  - Total bilirubin ≤ 2 times the upper limit of normal (ULN)
  - ALT and AST ≤ 2 times ULN
- Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.
- Ability to provide written informed consent

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Exclusion Criteria:

- Known history of active coronary artery disease, angina, myocardial infarction, congestive heart failure, cardiac arrhythmia or any other type of heart disease present within the last 6 months
- Known family history of hereditary heart disease
- QT interval corrected for rate (QTc) > 450 msec on the electrocardiogram (ECG) obtained at Screening
- Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes, with the exception of anti-microbials that are used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient
- Presence of active central nervous system (CNS) leukemia. Subjects adequately treated for CNS leukemia documented by 2 consecutive cerebrospinal fluid samples negative for leukemia cells are eligible. Subjects with no history of CNS leukemia will not be required to undergo cerebrospinal fluid sampling for eligibility.
- Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), or hepatitis C virus (HCV)
- Active infection requiring intravenous (IV) anti-infective usage within the last 7 days prior to study treatment
- Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results
- Pregnant or breast-feeding
- Treatment with any investigational product within 28 days prior to Screening

Criteria for Evaluation:

Safety: Safety will be assessed through the monitoring of adverse events (AEs), clinical laboratory parameters (hematology, serum chemistry, urinalysis), vital sign measurements, ECGs and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Efficacy: Efficacy assessment for AML will be performed using a modification of the recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Efficacy assessments for subjects with MDS or CMML will be performed using a modification of the International Working Group Response Criteria in Myelodysplasia. Efficacy assessments for any subject may be performed at other time points at the discretion of the investigator.

Pharmacokinetics: Pharmacokinetic determinations will be performed.

Pharmacodynamics: XMP will be determined in peripheral blood.

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Investigational Product:

FF-10501-01 is an oral antimetabolite anticancer drug. It is a competitive inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH). FF-10501-01 is supplied in 50 and 200 mg tablets for oral administration. FF-10501-01 should be stored at room temperature (20 – 25 °C).

FF-10501-01 is manufactured for FPHU by Patheon (Missisauga, Ontario, Canada) and will be provided by the sponsor (FPHU).

Reference Therapy: None

Statistical Methods:

Safety Endpoint Analyses:

Safety endpoints for AEs include the following: incidences of all treatment-emergent adverse events (TEAEs) and all serious adverse events (SAEs); incidences of TEAEs and SAEs by severity; incidences of TEAEs and SAEs by relationship to study medications; incidences of all Grade 3 and 4 TEAEs and by severity and relationship to study medications; and discontinuation of subjects from the study due to AEs or death. Safety endpoints for AEs, clinical laboratory tests, vital signs, ECGs and physical examinations will be specified in the statistical analysis plan. All safety endpoints will be summarized using descriptive statistics.

Efficacy Endpoint Analyses:

The primary endpoint will be the proportion of subjects who achieve an objective response (OR) as best response (CR, CRi or PR). Each dose cohort will be analyzed independently. For the primary efficacy endpoint, OR by disease type (AML, MDS, CMML) will be summarized using the number and percentage of subjects with an OR. The proportion of subjects with hematologic improvement in peripheral blood or bone marrow blast count and 90% confidence intervals will be estimated. For secondary endpoints, PFS and OS, curves will be estimated for each dose cohort and disease type using Kaplan-Meier product-limit estimates.

Pharmacokinetic and Pharmacodynamic Endpoint Analyses: Analysis plans will be described in the written plans provided by the laboratories performing the analyses.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6-MP	6-mercaptopurine
6-TG	6-thioguanine
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALT (SGPT)	Alanine transaminase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
Ara-C	Cytosine arabinoside
AST (SGOT)	Aspartate transaminase
BID	Twice a day
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
C_{max}	Peak concentration
CML	Chronic myelocytic leukemia
CMML	Chronic myelomoncytic leukemia
CNS	Central nervous system
CR	Complete remission/complete response
CRi	Complete remission with incomplete blood count recovery
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
dL	Decaliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
FPHU	FUJIFILM Pharmaceuticals, U.S.A., Inc.
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GTP	Glutamyl transpeptidase
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polyethylene
HI	Hematologic improvement
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
ICD	Informed consent document
ICH	International Conference on Harmonisation

Abbreviation	Definition
IMPDH	Inosine 5'- monophosphate dehydrogenase
IND	Investigational New Drug
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System Revised
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liter
LD_{10}	Lethal dose 10%
m^2	Meters squared
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
mg	Milligram
mL	Milliliter
NCI	National Cancer Institute
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression-free survival
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial remission/partial response
Q	Every
QTc	QT interval corrected for rate
RBC	Red blood cell
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TID	Three times a day
T_{max}	Time to peak concentration
U	Units
ULN	Upper limit of normal
WBC	White blood cell
WCBP	Woman of child-bearing potential
WHO	World Health Organization
XMP	Xanthosine monophosphate

1. INTRODUCTION

1.1. FF-10501-01 Background

FF-10501-01 (5-hydroxy-1*H*-imidazole-4-carboxamide 3/4 hydrate), is the ¾ hydrate of FF-10501, an oral antimetabolite anticancer agent. It is a potent competitive inhibitor of inosine 5'- monophosphate dehydrogenase (IMPDH), a key enzyme involved in de novo purine synthesis, and inhibits deoxyribonucleic acid (DNA) synthesis of guanine monophosphate from xanthosine monophosphate. The chemical structure and mechanism of action of FF-10501 is depicted in **Figure 1**.

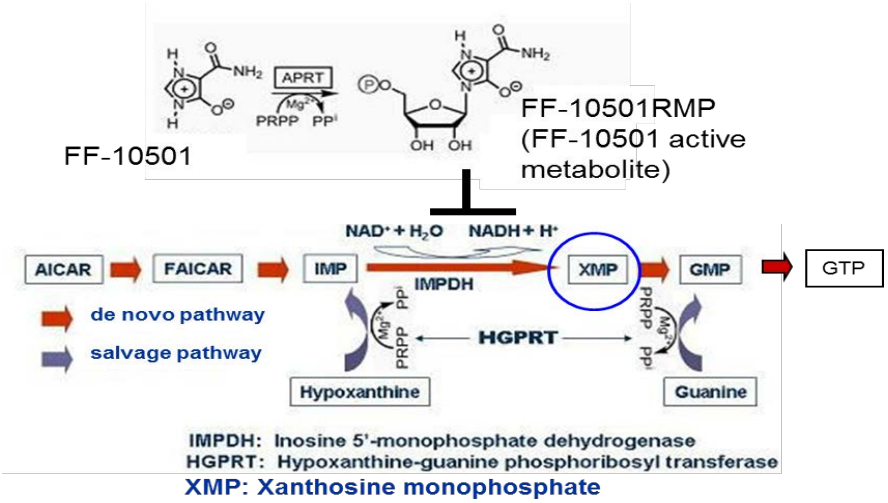

Figure 1. FF-10501 Structure and Mechanism of Action

FF-10501-01 contains the same active pharmaceutical ingredient as SM-108, a compound discovered in the 1980s and developed through Phase 1 and 2 clinical studies by Sumitomo Chemical Co. FF-10501-01 drug substance is manufactured identically to SM-108, but the synthetic process was improved to increase the purity of FF-10501-01, which ensures better drug substance stability and a more stable FF-10501-01 drug product. SM-108 is the compound designation for studies previously conducted by Sumitomo. FF-10501-01 was used as the test article in all studies conducted under the direction of FUJIFILM.

1.2. SM-108 Preclinical Summary

SM-108 was found to have a different spectrum of activity from conventional antipurinergic agents, 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG). Most notably, SM-108 demonstrated collateral sensitivity with greater therapeutic effect on a 6-MP-resistant murine leukemia cell line, P388, than on 6-MP-sensitive strains. Among murine experimental tumors, Ehrlich carcinoma, sarcoma 180, Lewis lung carcinoma, colon 26, colon 38, L1210 and P388 were highly responsive to SM-108, especially following intermittent administrations per day, rather than daily administration and inhibited the growth of selected human tumor cell lines derived from hematologic malignancies and some solid tumors (lung, prostate cancers and choriocarcinoma).[1,2,3,4]

The lethal dose 10% (LD_{10}) following oral administration to mice for 5 days was 4800

mg/m^2/day with QD dosing, 2610 mg/m^2/day with TID dosing (Q 4 hours only in daytime), and 135 mg/m^2/day with TID dosing (Q 8 hours).[5]

Teratology studies previously conducted by Sumitomo in the mouse, rat and rabbit were positive.[6] This is not an unexpected finding for cytotoxic agents used as anticancer treatment, and precautions will be taken to avoid pregnancy in the proposed clinical study.

1.3. SM-108 Previous Human Experience

A total of three SM-108 clinical studies in patients with hematologic malignancies or lung cancer were previously conducted by Sumitomo in the 1980s at doses ranging from 20 to 2500 mg/m^2. The majority of the Phase 2 study dose regimens were 100-300 mg/m^2 BID (200 to 600 mg/m^2/day). A total of 265 patients were treated in these studies and efficacy was seen in patients with hematologic malignancies.

1.3.1. Phase 1 Study in Advanced Solid Tumors or Hematologic Malignancies

In a Phase 1 study of oral SM-108 in patients with advanced solid tumors or hematologic malignancies, 73 patients were treated on a 5-day consecutive schedule at doses ranging from 20 to 2500 mg/m^2.[5] Adverse events were reported in 23 of 73 patients (31.5%), however a correlation between adverse events and dose was unclear. The maximum tolerated dose (MTD) and doses eliciting dose-limiting toxicity (DLT) were not determined. The most common adverse events reported were gastrointestinal; nausea (11 patients, 15%), anorexia (7 patients, 10%), emesis (5 patients, 7%). Elevated AST (to > 45 U), ALT (to > 50U) and uric acid (to ≥ 8 mg/dL) also were noted in some patients. In 31 patients with hematologic malignancies enrolled in the study, 2 of 3 patients with atypical leukemia achieved a complete response, and 2 of 12 patients with acute myeloid leukemia (AML) and 1 of 1 patient with acute lymphocytic leukemia (ALL) achieved a partial response (PR). Mean days to response ranged from 12 to 18 days. No responses were noted in the 42 patients with solid tumors.

A dose-dependent increase in serum levels of SM-108 were observed up to 2000 mg/m^2/day, with time to peak serum concentration (T_{max}) of 2 hours at ≤ 100 mg/m^2 and T_{max} of 4 hours at doses ≥ 240 mg/m^2. A total of 40 – 60% of the administered drug was excreted in active form in the urine over 24 hours post-dose, suggesting primary renal elimination.

1.3.2. Phase 2 Study in Advanced Lung Cancer

In an early Phase 2 study, 27 patients with advanced lung cancer (primarily adenocarcinoma) received SM-108 at oral doses of 200 mg/m^2 BID or TID (400 or 600 mg/m^2/day) for ≥ 2 weeks (400 mg/m^2/day) or for ≥ 4 weeks (600 mg/m^2/day).[5] One patient achieved a minor response at a dose of 600 mg/m^2/day). No true objective responses (ORs) were observed. The most commonly reported adverse events were gastrointestinal (anorexia, malaise, nausea/emesis), in 4 of 12 (33%) and 6 of 15 (40%) of patients receiving 400 and 600 mg/m^2/day, respectively. The incidence of hematological adverse events (neutropenia, thrombocytopenia and decreased hemoglobin [Hb]) was 2 of 12 (17%) and 4 of 15 (27%) of patients receiving 400 and 600 mg/m^2/day, respectively. Nadirs occurred

at approximately 4 -6 weeks of treatment in both groups, and return to baseline parameters was noted within 2 weeks.

1.3.3. Phase 2 Study in Advanced Hematologic Malignancies

A larger Phase 2 study was conducted in patients with advanced hematologic malignancies.[7] A total of 165 patients were enrolled; 85 had received prior therapy with antimetabolites, including 6-MP or cytosine arabinoside (ara-C). Patients were treated with SM-108 orally, at doses of 70, 200 or 300 mg/m^2 BID (140, 400 or 600 mg/m^2/day). In 39 patients with chronic myelogenous leukemia (CML), 21 had complete responses (CRs) and 6 had PRs for an OR rate of 69%. Among 30 patients with AML, 7 had PRs (23%). Among 36 patients with MDS, 1 had a CR, 12 had PRs for an ORR of 36%. For 13 patients with polycythemia rubra, 4 had CRs and 7 had PRs for an ORR of 84.6%). The RR rate was highest in patients with CML and MDS at doses of ≥ 600 mg/m^2/day. Clinical responses by dose are described in **Table 1**.

Table 1. Phase 2 Study in Hematologic Malignancies: Clinical Response by Dose

Diagnosis / Dose (mg/day)	CML	MDS				Polycythaemia vera	AML	Total (%)
		CMMoL	RAEB	RAEB in T	Total			
< 200			1/2		½		0/2	1/4 (25)
200 to < 400	1/1	1/1	0/1	0/3	1/5	2/2	1/3	5/11 (45.5)
400 to < 600	2/4	0/1	2/7	0/3	2/11	3/3	2/11	9/29 (31)
600 to < 800	20/22	4/7	2/3	2/4	8/14	6/8	2/10	36/54 (66.7)
800 to < 1000	4/11	0/2	0/1	1/1	¼		2/4	7/19 (36.8)
1000 ≤	0/1							0/1
Total (%)	27/39 (69.2)	5/11 (45.5)	5/14 (35.7)	3/11 (27.3)	13/36 (36.1)	11/13 (84.6)	7/30 (23.3)	58/118 (49.1)

The most commonly reported adverse events were gastrointestinal (nausea, anorexia, vomiting, abdominal discomfort; 66%), followed by allergic symptoms (rash, pruritis; 1%). Changes in laboratory values occurred in 30 of 165 (18%) of patients, all were transient/reversible and most were ≤ Grade 2. A total of 14 patients (8%) experienced bone marrow suppression (neutropenia, thrombocytopenia, reduced Hb). The nadir was reached in 2 -3 weeks for white blood cell (WBC) count and platelets, 5 weeks for Hb, and recovery from nadir to pre-dose values was approximately 2 weeks **(Table 2).**

Table 2. Phase 2 Study Hematologic Malignancies: Adverse Events in ≥ 2% Patients

Total Number of Patients		165
Number of Patients Reporting (%)	Increased ALT	16 (9.7)
	Nausea	15 (9.1)
	Increased AST	14 (8.5)
	Loss of appetite	11 (6.7)
	Decreased platelet count	8 (4.8)
	Rash	7 (4.2)
	Vomiting	6 (3.6)
	Decreased hemoglobin	4 (2.4)
	Abdominal discomfort	3 (1.8)
	General malaise	3 (1.8)
	Decreased WBC	3 (1.8)
	Increased total bilirubin	3 (1.8)
	Increased GTP	3 (1.8)

1.4. FF-10501-01 Preclinical Pharmacology

1.4.1. Induction of differentiation in myeloid leukemia cell lines

In the K562 human myeloid leukemia cell line, FF-10501-01induced the expression of fetal hemoglobin (HbF) over a concentration range of 1 to 1000 µmol/L in a dose-dependent manner.[8] Increased HbF production in K562 cells is a measure of reactivation of fetal Hb production in K562 cells, hence a measure of induction of cell differentiation (**Figure 2**).

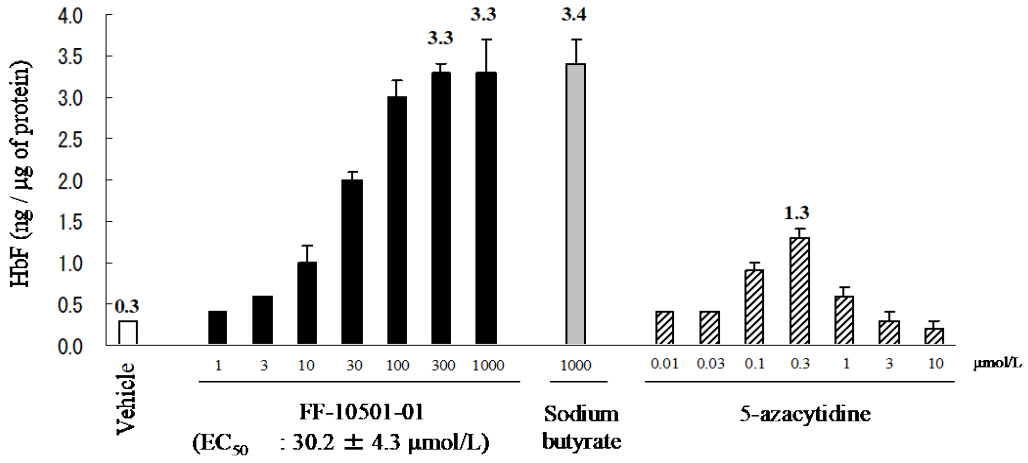

Figure 2. Induction and Expression of HbF in K562 Human Myeloid Leukemia Cell Line Treated with FF-10501-01, Sodium Butyrate or Azacitidine

FF-10501-01 also induced the expression of the CD235a and CD11b cell surface antigens in a dose-dependent manner in the K562 and MOLM-13 human myeloid leukemia cell lines, respectively.[9] Increased CD235a (glycophorin A) and CD11b (CR3) are used as measures of induction of cell differentiation (**Figure 3**).

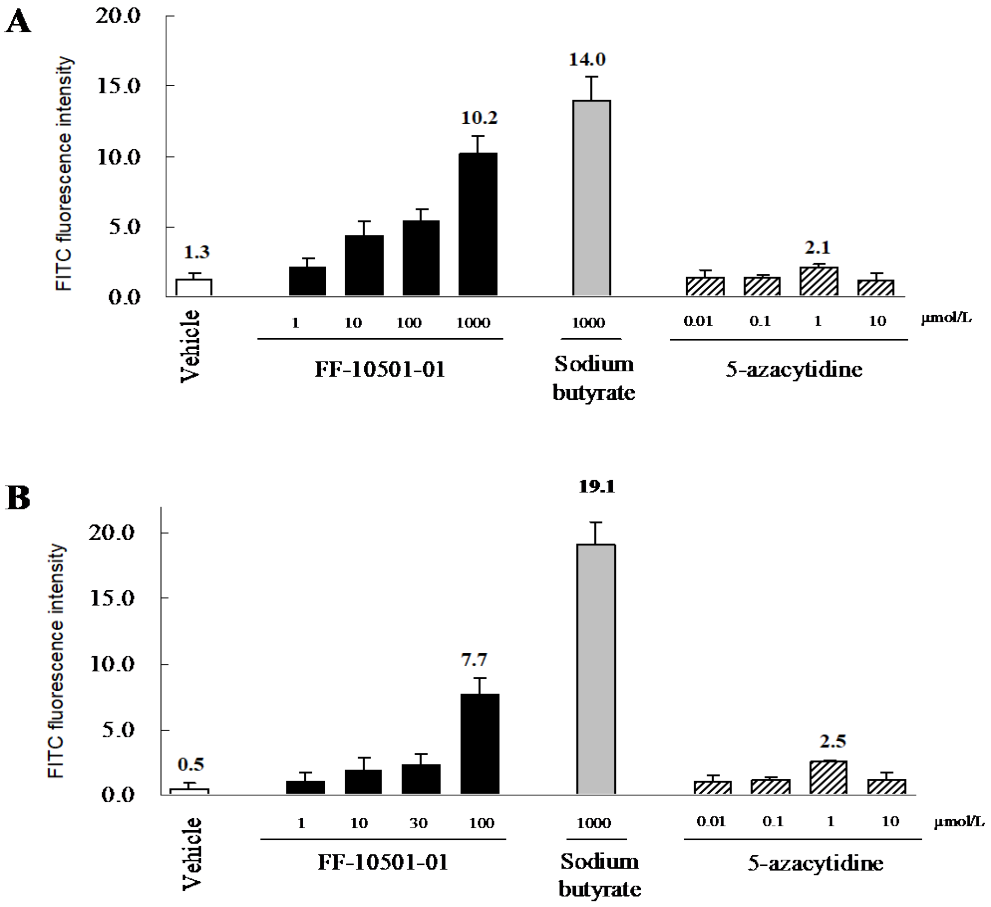

Figure 3. Induction and Expression of Cell Surface Antigens in the K562 (A) and MOLM-13 (B) Human Myeloid Leukemia Cell Lines Treated with FF-10501-01, Sodium Butyrate or Azacitidine

1.4.2. In Vitro Growth Inhibition in Myeloid Leukemia Cell Lines

FF-10501-01 inhibited the growth of the five human myeloid leukemia cell lines MOLM-13, SKM-1, HNT-34, OCI-M2, and K562 at mean IC_{50} levels of 7.8, 21.5, 51.9, 204.2, and 10.7 μmol/L, respectively (**Table 3**).[10]

Table 3. Cell Growth Inhibition by FF-10501-01 and Azacitidine on Human Myeloid Leukemia Cell Lines

Cell line	IC_{50} (μmol/L)	
	FF-10501-01	Azacitidine
MOLM-13	7.8 ± 0.6	0.7 ± 0.1
SKM-1	21.5 ± 2.6	1.7 ± 0.1
HNT-34	51.9 ± 3.8	2.0 ± 0.2
OCI-M2	204.2 ± 20.6	2.0 ± 0.1
K562	10.7 ± 1.0	2.4 ± 0.1

1.4.3. Inhibition of Growth in an Azacitidine-resistant Cell Line

An azacitidine-resistant cell line was produced with the SKM-1 human myeloid leukemia cell line (SKM-1/AR).[11] The ability of FF-10501-01 to inhibit the growth of the parent and resistant lines was investigated. The IC_{50} of FF-10501-01 in the resistant cell line was 9.49 µmol/L versus 36.27 and > 700 µmol/L for azacitidine and 5-aza-2'-deoxycytidine (decitabine), respectively (**Table 4**).

Table 4. Cell Growth Inhibition by FF-10501-01, Azacitidine and Decitabine in Azacitidine-resistant Cell Line (SKM-1/AR)

Cell line	IC_{50} (µmol/L)		
	FF-10501-01	Azacitidine	Decitabine
SKM-1	23.47 ± 2.32	1.85 ± 0.09	0.13 ± 0.01
SKM-1/AR	9.49 ± 0.42	36.27 ± 0.17	> 700

1.4.4. FF10501-01 Mechanism of Action

At concentrations of 1 to 1000 nmol/L, the active form of FF-10501 (monosodium salt, FF-10501 ribosyl monophosphate [FF-10501RMP-Na]) inhibited the enzymatic activity of human inosine 5′-monophosphate dehydrogenase (IMPDH) 1 and IMPDH2.[12] IC_{50} values were 29.0 and 31.8 nmol/L, respectively, versus 26.4 and 27.8 nmol/L for mycophenolic acid. FF-10501-01 inhibited IMPDH1 and IMPDH2 by 5.6% and −11.1%, respectively, at a concentration of 10000 nmol/L (**Table 5**).

Table 5. Inhibition of Human IMPDH1 and IMPDH2 by FF-10501RMP-Na, FF-10501-01 and Mycophenolic Acid

Enzyme	IC_{50} (nmol/L)		Enzyme activity inhibition at 10000 nmol/L (%)
	FF-10501RMP·Na	Mycophenolic acid	FF-10501-01
Human IMPDH1	29.0 ± 10.3	26.4 ± 1.5	5.6 ± 16.6
Human IMPDH2	31.8 ± 5.6	27.8 ± 8.3	-11.1 ± 9.8

In the SKM-1 human myeloid leukemia cell line, FF-10501-01 lowered intracellular GTP levels in a dose-dependent manner at concentrations of 1 to 100 µmol/L (**Figure 4**).[13]

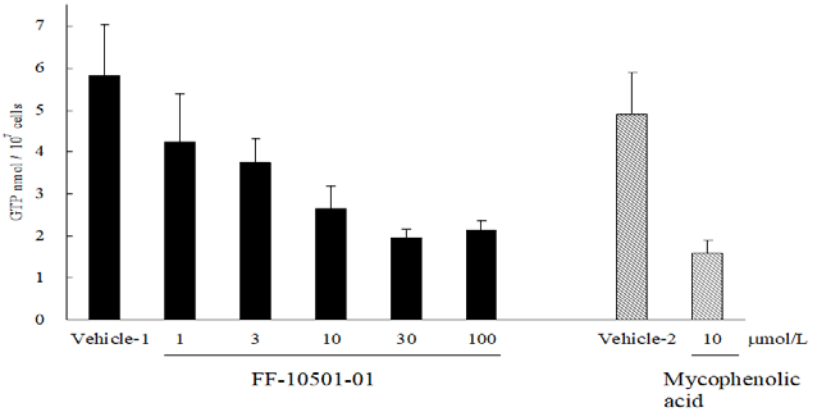

Figure 4. Effect on Intracellular GTP Levels in SKM-1 Human Myeloid Leukemia Cell Line Treated with FF-10501-01 or Mycophenolic Acid

1.4.5. Anti-tumor Activity in a Human Myeloid Leukemia SKM-1 Xenograft Model in Mice

In mice subcutaneously injected with the SKM-1 human myeloid leukemia cell line, FF-10501-01 significantly inhibited the growth of tumors when orally administered at 480 mg/kg/day (5 cycles consisting of 3 daily doses x 2 days followed by 4 days rest x 5 cycles) as did azacitidine at 5 mg/kg/day ($p<0.05$).[14] Transient post-administration weight loss was observed in all groups dosed with FF-10501-01 and azacitidine (**Figure 5**). The arrows indicate daily dosing relative to body weight determination.

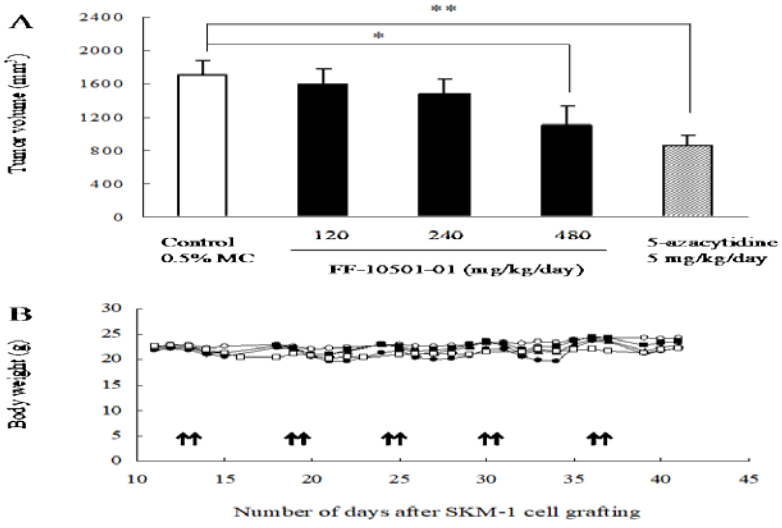

Figure 5. Anti-tumor and Body Weight Data in a Human Myeloid Leukemia SKM-1 Xenograft Model in Mice Treated with FF-10501-01 or Azacitidine

1.5. FF-10501-01 Preclinical Pharmacokinetic, Metabolism, Excretion

1.5.1. Single Oral Dose Pharmacokinetics

FF-10501-01 was administered once orally at FF-10501 (free form) doses of 10, 40, 80, or 160 mg/kg to non-fasted female mice demonstrated that C_{max} and the area under the concentration-time curve (AUC_{0-24} and AUC) increased with increasing doses over the dose range of 10 to 160 mg/kg.[15] The increase was nearly dose proportional from 10 to 80 mg/kg and less than dose proportional from 80 to 160 mg/kg. The T_{max} was 0.5 hours for all dose groups. The terminal half-time ($t_{½}$) ranged from 1.3 to 2.5 hours and was not dose proportional.

Changes in plasma concentrations in fasted or non-fasted male rats after an oral or intravenous dose of 15 mg/kg of FF-10501-01 are shown in **Figure 6**. The bioavailability of FF-10501-01 in fasted and non-fasted rats was 51.7% and 39.5%, respectively, indicating that food effects are minimal.[16] Half-life was slightly longer in the non-fasted animals (2.2 hours) versus the fasted animals (1.5 hours).

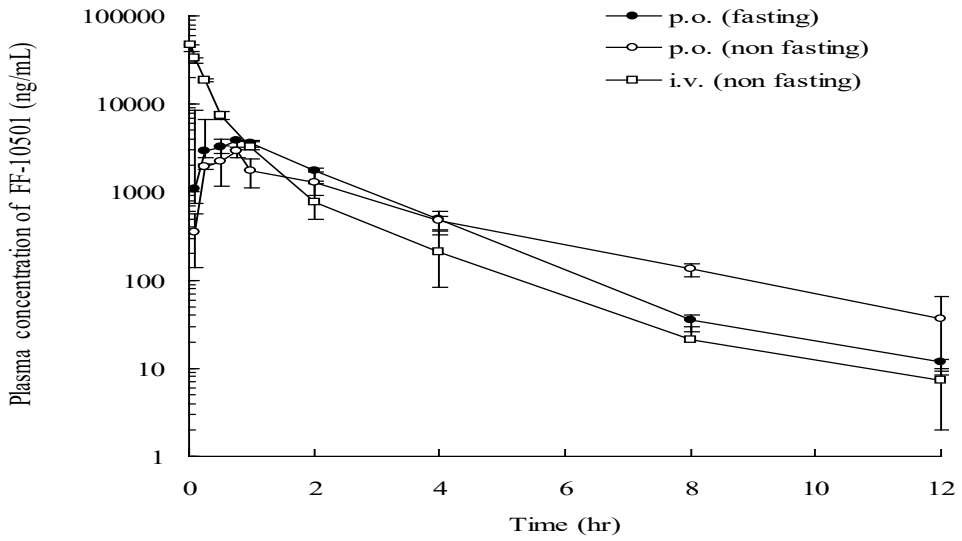

Figure 6. FF-10501 Plasma Concentrations in Fasted or Non-fasted Rats Following a Single Oral or Intravenous Dose

1.5.2. Multiple Dose Oral Pharmacokinetics

Once-daily doses of 0.6, 3, and 15 mg/kg of FF-10501-01 (doses in FF-10501 free form) were repeatedly orally administered to male and female rats for 1 month.[17] The C_{max} and AUC_{0-24} of FF-10501 on the first and last days of dosing increased in proportion to dose in the male and female animals. Systemic exposure to FF-10501 at the final dose was generally higher than at the first dose in both the male and female animals (0.8- to 2.6-fold higher). C_{max} and AUC_{0-24} at the first and last doses were generally higher in the females than in the males (1.0- to 2.2-fold higher).

As in the rats, the C_{max} and AUC_{0-24} of FF-10501 in male and female dogs upon repeated oral doses of 10, 30, or 100 mg/kg FF-10501-01 (doses in FF-10501 free form) once daily for 1 month increased in a dose-dependent manner.[18] $T_{½}$ was generally 3 – 4 hours in most groups, with females in the 100 mg/kg dose group exhibiting a $t_{½}$ of 7.5 hours after 28 days of repeat dosing. C_{max} and AUC remained relatively stable over the 28-day dosing period in all groups, demonstrating little evidence of accumulation.

1.5.3. Distribution

Radioactivity was widely distributed to the tissues of non-fasted male rats given a single oral dose of 15 mg/kg of ^{14}C-FF-10501-01.[19,20] Concentrations reached a maximum at 2 hours post-dose in most of the tissues. Disregarding the gastrointestinal tract, in which concentrated drug was expected due to the route of administration, the maximum concentrations in the kidneys and bladder were higher than plasma concentrations, but distribution to the cerebellum, cerebrum, and other central nervous system tissues was low. Concentrations in the other tissues were comparable to those in the plasma. The compound did not exhibit affinity for melanin-containing tissues. At 96 hours post-dose, only trace amounts of radioactivity were noted in the colon contents, but radioactivity was at or below the limit of detection in all tissues at this time.

Tissue distribution in the elimination phase was investigated in male dogs orally dosed with a single dose of 15 mg/kg of ^{14}C-FF-10501-01.[21] Levels were high in the liver at 48 and 72 hours postdose. The tissue-to-plasma ratio of radioactivity at these times was 15.14 and 11.91, respectively. At 72 hours postdose levels of radioactivity were, in comparison to the plasma, higher in all tissues other than the cerebellum, fat, pancreas, and testes, but radioactivity was eliminated over time in parallel with or more rapidly than the elimination from the plasma.

The serum protein binding of ^{14}C-FF-10501 was uniformly low in all species, ranging from 1.4% to 3.2% in mice, 0.8% to 3.4% in rats, 1.6% to 2.8% in dogs, and 0.7% to 1.6% in humans.[22]

1.5.4. Metabolism

Metabolites of FF-10501-01 in the plasma, urine, bile (rats only), and feces of rats and dogs were investigated.[21,23,24] The parent drug, FF-10501, the ribose form (M1), the glucuronic acid conjugate, the pyranoside form, and two sulfate conjugates were identified in the plasma and urine. Unknown metabolites were also identified in the plasma, urine, bile and feces.

In an investigation of inhibitory effects on human liver cytochrome P-450 isozyme activity (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), FF-10501-01 mildly inhibited the metabolic activity of each isozyme studied as evidenced by IC_{50}s of not less than 1240 μmol/L in each case.[25] Therefore, no drug-drug interactions are expected.

1.5.5. Excretion

In non-fasted male rats receiving a single oral dose of ^{14}C-FF-10501-01, 80.3%, 27.1%, and 2.5% of the radioactivity dosed was excreted in the urine, feces, and expiratory air,

respectively, by 72 hours post-dose.[26] Total cumulative excretion was 110.2%. The radioactivity excreted in the bile by 24 hours post-dose was only 1.0% of the amount dosed.

In non-fasted male dogs receiving a single oral dose of ^{14}C-FF-10501-01, 76.63% and 10.45% of the radioactivity dosed was excreted in the urine and feces, respectively, by 24 hours post-dose.[20] Moreover, 79.42% and 12.07% of the radioactivity dosed was excreted in the urine and feces by 72 hours post-dose. Total cumulative excretion was 97.33%.

Therefore, the kidney appears to be the major route of elimination (~80%) with a lesser amount of drug found in the feces (~10 – 20%).

1.6. Toxicology

1.6.1. Repeat-dose Toxicity Studies in Rats

A 2-week repeated oral dose toxicity study of FF-10501-01 (FF-10501 equivalent doses of 1, 5, 25 mg/kg/day) was conducted in rats.[27] At the dose of 25 mg/kg, suppressed body weight gain or weight loss, low food consumption, and gastrointestinal injury were observed, and two of the five males died. No abnormalities were noted with 1 mg/kg. Changes in hematological test values attributable to myelosuppression were observed at doses of 5 mg/kg and greater. The MTD was determined to be 5 mg/kg/day (30 mg/m^2/day).

No deaths were observed in a 2-week intermittent oral dose toxicity study in rats (3 cycles of FF-10501-01, as FF-10501 equivalent doses of 15, 45, 90, or 180 mg/kg oral doses once daily for 2 consecutive days followed by withdrawal for 4 days).[28] Suppressed body weight gain and myelosuppression were noted at the doses of 15 mg/kg and greater. Low food consumption and gastrointestinal injury were observed at doses of ≥ 90 mg/kg.

No deaths were observed in a 1-month repeated oral dose toxicity study of FF-10501-01 in rats (FF-10501 equivalent doses of 0.6, 3, 15 mg/kg/day).[17] No abnormalities were observed at 0.6 mg/kg. At doses of 3 mg/kg and greater, suppressed body weight gain and a low bone marrow nucleated cell count were noted. Low food consumption, changes in hematological test values attributable to myelosuppression, and gastrointestinal injury were observed at 15 mg/kg. Suppressed body weight gain and low food consumption were observed continuously until the end of the recovery period in the males dosed with 15 mg/kg, but the other changes recovered or showed tendencies toward recovery during a 1-month recovery period. The no observed adverse effect level in the 1-month repeated oral dose toxicity study in rats was 0.6 mg/kg/day. The MTD was determined to be 15 mg/kg/day (90 mg/m^2/day).

1.6.2. Repeat-dose Toxicity Studies in Dogs

In a 2-week repeat oral dose toxicity study of FF-10501-01 in dogs (FF-10501 equivalent doses of 10, 30, 100 mg/kg/day), no deaths were observed, and no abnormalities were observed at 10 mg/kg.[29] Gastrointestinal injury was observed at doses of 30 mg/kg and greater. In the 30 mg/kg group, histopathological examinations revealed slight cell debris in the crypt lumen of the duodenum and minimum single cell necrosis in the crypt epithelium of the colon and rectum. No abnormalities were noted in the other tests. In the 100 mg/kg group, soft stool, body weight loss, and low food consumption and weight loss were noted in one of the two animals, and the affected animal showed dark red area in the

mucosa of the ileum and cecum during necropsy. No toxicologically significant changes were noted in electrocardiography or other testing. In conclusion, gastrointestinal effects were observed at doses of 30 mg/kg and greater, and soft stool, body weight loss, and low food consumption were observed at 100 mg/kg in the study. The MTD was determined to be 100 mg/kg/day (2000 mg/m^2/day).

In a 1-month repeat oral dose toxicity study of FF-10501-01 in dogs (FF-10501 equivalent of 10, 30, 100 mg/kg/day), two of the five females dosed with 100 mg/kg were necropsied on Day 14 of dosing because of moribund condition.[18] No abnormalities were observed at 10 mg/kg. Gastrointestinal injury was observed at doses of 30 mg/kg and greater. Low food consumption and weight loss were noted at 100 mg/kg. In the recovery study, soft stool, which was noted during the treatment period, resolved on Day 5 of recovery (Day 1 of recovery is the day after the final dose). Body weight and food consumption rapidly recovered. The histopathological changes in the gastrointestinal tract and other changes observed during the dosing period had recovered or showed tendencies toward recovery in the tests performed at the end of the recovery period. In conclusion, gastrointestinal injury was observed in the males and females of the groups receiving 30 mg/kg or greater. The MTD was determined to be 30 mg/kg/day (600 mg/m^2/day).

The dog proved to be the more relevant of the species regarding the tolerability of FF-10501-01, as demonstrated in previous human clinical studies of SM-108.

1.6.3. Genotoxicity

Negative results were obtained in bacterial reverse mutation assays.[30]

In vitro chromosomal aberration tests performed in a cell line derived from Chinese hamster lung (CHL/IU cells) showed that FF-10501-01 induced chromosomal aberrations both with and without metabolic activation.[31]

1.6.4. Phototoxicity

The findings of visible-ultraviolet absorption spectrometry of FF-10501-01 indicate a low potential for phototoxicity.[32]

Additional information can be found in the FF-10501-01 Investigator's Brochure.

1.7. FF-10501-01 Experience in Humans

1.7.1. Japan Phase 1 Study

A Phase 1 study of FF-10501-01 conducted by FUJIFILM (Toyama Chemical) in Japan in patients with MDS, was completed. In this study, patients received FF-10501-01 at doses of 200, 300 and 400 mg BID (400, 600 and 800 mg/day) for 14 days continuously followed by 14 days off therapy (28-day cycle).[33] A total of 9 patients were treated. No DLTs were observed. One study drug-related serious adverse event (SAE) (Grade 4 neutropenia) occurred in Cycle 1 in one subject treated with FF-10501 800 mg/day. Two study drug-related SAEs (Grade 3 anemia and Grade 3 pneumonia) occurred in Cycle 5 in two subjects treated with FF-10501 400 mg/day. The most common adverse events (AEs) in all patients, regardless of causality, were anemia, rash, and platelet count decreased (33.3%, 3 of 9

subjects each). The treatments after cycle 1 were extended in 8 patients out of 9 in each treatment cohort; 3 at 400 mg/day, 3 at 600 mg/day and 2 at 800 mg/day.

The median number of treatment cycles were 4 (range 2-5) at 400 mg/day, 13 (range 2-18) at 600 mg/day, and 2 (range 1-7) at 800 mg/day. One patient at 600 mg/day has received a total of 18 cycles to date and remains on study. C_{max} and AUC increased with increasing FF-10501-01 dose. T_{max} was 2 to 4 hours and the drug was nearly eliminated within 24 hours after administration. The cumulative urinary excretion rate of FF-10501 up to 24 hours after administration was 25 to 45%. No accumulation of FF-10501 was observed.

1.7.2. U.S. Phase 1/2a Study

Study FF1050101US101 is ongoing in the United States in patients with AML, MDS or CMML. In Phase 1, dose levels of 50, 100, 200, 300, 400 and 500 mg/m^2 BID for 14 days, followed by 14 days off therapy, or 400 mg/m^2 BID for 21 days, followed by 7 days off therapy, repeated every 28 days have been studied to date. A total of 33 patients have been treated to date on study (25 AML, 8 MDS).

Three events of drug-related atrial fibrillation (Grade 2) were reported in 2 subjects at a dose of 500 mg/m^2 BID (Cohort 6). Study drug was suspended in both subjects and all events resolved with oral metoprolol treatment. These events were medically important events and thus met the definition of dose-limiting toxicity (DLT). No further enrollment was made at this dose level. The maximally tolerated dose (MTD) was declared at 1 dose level below the dose eliciting DLT, 400 mg/m^2 BID, and this cohort was expanded to 6 subjects. No DLTs have been observed in N=7 total subjects treated at 400 mg/m^2 BID x 14 days.

At the MTD of 400 mg/m^2 BID, Cohort 7 was added to extend the BID dosing schedule to 21 days followed by 7 days off, repeated every 28 days (=1 cycle) (Amendment 3). No DLTs occurred have occurred to date.

At the MTD of 400 mg/m^2 BID, Cohort 8 was added to extend the BID dosing schedule to 28 days continuous dosing (=1 cycle) (Amendment 4). No DLTs have occurred to date.

The median number of prior treatments is 2 (range 1 - 7), all relapsed or refractory to prior hypomethylating agents (azacitidine, decitabine). The median number of treatment cycles is 2 (range 1 – 28).

The most common AEs include Grade 1 or 2 fatigue, diarrhea, and nausea, with drug-related Grade 3 or 4 AEs reported for 1 patient in the 200 mg/m^2 BID dose group (thrombocytopenia, neutropenia and bone marrow aplasia) and 1 patient in the 300 mg/m^2 BID dose group (mucositis); the events resolved without sequelae.

Partial remissions have occurred in 3 AML patients (50, 100 and 400 mg/m^2 BID) after 1 – 3 cycles, lasting for at least 28, 5 and 6 cycles, respectively. A total of 8/25 (32%) AML patients, including the 3 PRs, have attained stable disease control with no disease progression over 4 – 28 cycles. A marrow complete response was achieved in 1 MDS patient treated at 400 mg/m^2 BID x 14 days after 1 cycle and was sustained for 14 cycles. A major platelet response was observed in 1 patient treated at 400 mg/m^2 BID x 21 days, sustained for 1 cycle. Four of 8 MDS patients (50%), including the marrow CR, attained stable disease control with no disease progression over 3, 5, 14 and 17 cycles, respectively.

FF-10501-01 was rapidly absorbed with mean T_{max} of 2.74 hours and mean $t_{½}$ of 4.05 hours. Drug exposure ($AUC_{0–24}$ and AUC_{course}) increased with dose in a near linear manner.

Potent suppression of circulating xanthosine monophosphate (XMP), a marker of IMPDH activity, has been observed following FF-10501-01 administration on Day 1 of Cycles 1 and 2 at doses ≥ 50 mg/m^2 BID.

1.8. Dose Rationale

In the SM-108 Phase 2 study described above, patients with hematologic malignancies showed responses at oral doses of 200 – 300 mg/m^2 BID (400 – 600 mg/m^2/day) administered for 14-day cycles. The toxicology findings in repeat dose studies in the rat and dog indicate a dose of 15 mg/kg (equivalent to 90 mg/m^2) in the rat for up to 1 month was well-tolerated with few effects, and a dose of 10 mg/kg (equivalent to 200 mg/m^2) in the dog up to 1 month exhibited no adverse effects. The dog appears to be the more relevant toxicology species based on prior human safety experience. Therefore, the starting dose in this study will be 50 mg/m^2 BID, which represents a 4-fold margin of safety over the MTD in the dog, escalating to 500 mg/m^2 BID, administered orally in 14-day cycles.

Since the study started, FF-10501-01 has been found to be well-tolerated up to a dose of 400 mg/m^2 BID orally x 28 days continuous dosing. Long-term stable disease has been observed in some MDS and AML patients (up to 28 cycles), as noted above.

The regimen for phase 2 is 400 mg/m^2 BID x 21 days out of a 28-day cycle.

2. STUDY OBJECTIVES

2.1. Primary Objective:

- To determine the safety and tolerability in subjects who receive FF-10501-01 for the treatment of advanced hematologic malignancies

2.2. Secondary Objective:

- To determine the overall response rates
- To evaluate the proportion of subjects who achieve hematologic improvement in peripheral blood or bone marrow blast count
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To evaluate the pharmacokinetics of FF-10501 and M1
- To evaluate the xanthosine monophosphate (XMP) as a pharmacodynamic marker

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 1/2a, dose-escalation study of FF-10501-01 for the treatment of advanced hematologic malignancies.

A total of up to N=68 subjects will be enrolled in the study. Subjects with acute myelogenous leukemia (AML) (Phase 1 only), myelodysplastic syndrome (MDS), and chronic myelomonocytic leukemia (CMML) will be included.

Major selection criteria are: age ≥ 18 years, confirmed MDS/CMML or AML (Phase 1 only for AML) with documented disease progression following previous therapy, or subjects with AML ≥ 60 years of age who are not candidates for other therapies (Phase 1 only). Subjects must be ≥ 3 weeks beyond chemotherapy, radiotherapy, major surgery, or other experimental treatments, and recovered from all acute toxicities (≤ Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1:

14-day Schedule: Following Screening, a total of 6 cohorts of 3 subjects each received oral doses of 50, 100, 200, 300, 400 or 500 mg/m^2 BID per day (100, 200, 400, 600, 800 or 1000 mg/m^2/day) for 14 days, followed by 14 days off, repeated every 28 days (= 1 cycle). Three events of drug-related atrial fibrillation (Grade 2) were reported in 2 subjects at a dose of 500 mg/m^2 BID (Cohort 6). Study drug was suspended in both subjects and all events resolved with oral metoprolol treatment. These events were medically important events and thus met the definition of dose-limiting toxicity (DLT). No further enrollment was made at this dose level. The maximally tolerated dose (MTD) was declared at 1 dose level below the dose eliciting DLT, 400 mg/m^2 BID, and this cohort was expanded to 6 subjects. No DLTs have been observed in N=7 total subjects treated at 400 mg/m^2 BID x 14 days.

21-day Schedule: At the MTD of 400 mg/m^2 BID, Cohort 7 was added to extend the BID dosing schedule to 21 days followed by 7 days off, repeated every 28 days (=1 cycle) (Amendment 3).

28-day Schedule: At the MTD of 400 mg/m^2 BID, Cohort 8 was added to extend the BID dosing schedule to 28 days continuous dosing each 28 days (= 1 cycle) (Amendment 4).

DLT is defined as Grade 4 hematologic toxicity lasting 7 days or more; Grade 3 nonhematologic toxicity of any duration not amenable to supportive care; failure of platelets, absolute neutrophil count (ANC), or hemoglobin (Hb) to recover to Grade 1 within 12 weeks despite use of platelet and red blood cell (RBC) transfusions and/or growth factors; febrile neutropenia (defined as ANC<1000/mm^3 with a single temperature of > 38.3°C or sustained temperature of ≥ 38°C for over one hour); Grade 3 thrombocytopenia associated with bleeding; or other important medical event.

For all subject cohorts, if 1 of 3 subjects per cohort experiences DLT, the cohort will be expanded to 6. If 2 of 6 subjects per cohort experience DLT, all further dose escalation will stop. If 0 of 3 or ≤ 1 of 6 subjects per cohort experience DLT by Day 28 following dosing of FF-10501-01, dose escalation will proceed to the next cohort. At the MTD of 400 mg/m^2 BID, the longest schedule of administration below the schedule of administration eliciting

DLT will be declared the recommended Phase 2 dose (RP2D) and schedule. A total of 6 subjects will be treated at the RP2D and schedule. No intra-subject dose escalation will be allowed from previous dose levels/schedules of administration until at least one subject has completed Cycle 1 at the longer schedule of administration (e.g., 21 or 28 days) with no Grade 2 or greater toxicities observed.

Additionally, patients currently on study will have the option to extend their current dosing schedule to 21 days, followed by 7 days off, repeated every 28 days (=1 cycle) or 28 days of continuous dosing, whichever is chosen as the best schedule, if seen in the patient's best interest by the principal investigator. Dose level adjustments for DLT will be made. Subjects who experience DLT at the first dose level, 50 mg/m^2 BID, will not be dose-reduced. Up to 48 subjects are planned for Phase 1.

Phase 2a: Once 6 subjects are treated at the RP2D and schedule in Phase 1, 1 additional cohort will enroll 20 subjects with MDS/CMML who have relapsed from, or are refractory to, prior hypomethylating agent (HMA) therapy. Subjects enrolled in Phase 1 at the RP2D and schedule and who meet the Phase 2a selection criteria will count towards the Phase 2a accrual. Dose level adjustments for adverse events will be made.

During the study, a Safety Review Committee, consisting of the actively recruiting investigators, the Medical Monitor, and FPHU, will review data from each cohort on an ongoing basis.

Subjects on the 21-day schedule will receive FF-10501-01 on a BID schedule. For all subjects on the 21-day dosing schedules, blood samples for pharmacokinetic assessment of FF-10501 and M1 in plasma will be collected on Cycle 1 Day 1 pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose, and Day 15 pre-dose (within 15 minutes prior to dosing), between 0.5-1 hr post-dose, and between 2-4 hr post-dose.

Blood concentration of xanthosine monophosphate (XMP) will be assessed as a pharmacodynamic endpoint.

For subjects on the 21-day dosing schedules, blood samples for XMP assessment will be collected on Cycle 1 Day 1 pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose, and Day 15 pre-dose (within 15 minutes prior to dosing), between 0.5-1 hr post-dose, and between 2-4 hr post-dose.

Disease assessments, including analysis of blood and bone marrow aspirates, will be performed at the end of Cycle 1 and Cycle 3 and every 2 cycles thereafter. Disease assessments may be performed at other time points at the discretion of the investigator.

Subjects who demonstrate objective response (OR) or stable disease (SD) will be allowed to continue therapy with FF-10501-01 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the subject's condition that prevents further study participation.

Blood for hematology, platelet and serum chemistry determinations will be collected within 28 days of Cycle 1 Day 1, on Days 1, 8, 15, and 22 of Cycle 1, on Day 1 of each subsequent cycle, and at the End of Study Visit. Urine will be collected for urinalysis within 28 days of Cycle 1, on Day 1 of each subsequent cycle and at the End of Study Visit.

Safety will be assessed through the monitoring of adverse events (AEs), clinical laboratory parameters (hematology, serum chemistry), vital sign measurements, electrocardiograms (ECGs) and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Efficacy assessment for AML will be performed using a modification of the recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Efficacy assessments for subjects with MDS or CMML will be performed using a modification of the International Working Group Response Criteria in Myelodysplasia. Efficacy assessments for any subject may be performed at other time points at the discretion of the investigator.

Pharmacokinetic determinations will be performed.

XMP will be determined in peripheral blood as a pharmacodynamics endpoint.

3.2. Number of Subjects and Centers

Phase 1: Up to 48 subjects are planned for the dose-escalation phase. Phase 2a: A total of 20 subjects with MDS/CMML treated at the RP2D are planned, including MDS/CMML subjects treated at the RP2D in Phase 1. Therefore, up to 68 subjects are planned.

The study will be conducted at up to seven sites.

3.3. Duration of Study

The accrual phase for the Phase 1 dose-escalation phase is expected to be 12 – 18 months. The expected accrual phase for the Phase 2a expansion phase is expected to be 6 – 12 months, with the last subject followed for up to 6 months, for a total study duration of 30 – 36 months. The anticipated accrual rate for the Phase 2a portion is 4 – 5 subjects per month.

3.4. Criteria for Termination of the Study

If the sponsor, investigator, study monitor, or officials from the Food and Drug Administration (FDA) discover conditions arising during the study that indicate that the study should be halted or that the study site should be terminated, this action may be taken after appropriate consultation between the sponsor and investigator.

Conditions that may warrant termination include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of an investigator to enroll subjects into the study at an acceptable rate

- Failure of an investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the study site to the sponsor, study monitor, or the FDA
- Insufficient adherence to protocol requirements

Study termination and follow-up would be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to participate in the study:

- Males and females ≥ 18 years of age
- Subjects with confirmed hematologic malignancies:
  - Phase 1:
    - High-risk MDS/CMML (defined as ≥ 10% peripheral blood or marrow blasts and/or International Prognostic Scoring System [IPSS][34] score ≥ 1.5) and relapsed or refractory to prior therapy
    - AML relapsed or refractory to prior therapy, or ≥ 60 years of age and not a candidate for other therapies
  - Phase 2a:
    - MDS/CMML, relapsed from, or refractory to prior HMA therapy; the latter defined as failure to achieve clinical remission (CR), partial remission (PR) or hematologic improvement (HI) after previous HMA therapy (≥ 4 cycles of azacitidine or decitabine), or progression during, or toxicity to, previous HMA therapy precluding further HMA treatment, and
    - Bone marrow blast count ≥ 10% or peripheral blast count ≥ 5%, or IPSS-R[35] score ≥ 3.5
- At least 3 weeks beyond the last chemotherapy, targeted anticancer agent, major surgery or experiment treatment and recovered from all acute toxicities (≤ Grade 1). *Hydroxyurea used to control peripheral blast counts is permitted up to Day 7 of treatment on study.*
- Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2
- Adequate renal and hepatic function:
  - Creatinine ≤ 2.0 mg/dL, or calculated creatinine clearance ≥ 45 mL/minute per the Cockcroft-Gault formula
  - Total bilirubin ≤ 2 times the upper limit of normal (ULN)
  - ALT and AST ≤ 2 times ULN

- Negative serum pregnancy test within 14 days prior to first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of the study treatment.
- Ability to provide written informed consent

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

- Known history of active coronary artery disease, angina, myocardial infarction, congestive heart failure, cardiac arrhythmia or any other type of heart disease present within the last 6 months
- Known family history of hereditary heart disease
- QT interval corrected for rate (QTc) > 450 msec on the electrocardiogram (ECG) obtained at Screening
- Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes with the exception of anti-microbials that are used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient
- Presence of active central nervous system (CNS) leukemia. Subjects adequately treated for CNS leukemia documented by 2 consecutive cerebrospinal fluid samples negative for leukemia cells are eligible. Subjects with no history of CNS leukemia will not be required to undergo cerebrospinal fluid sampling for eligibility.
- Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence with study requirements
- Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), or hepatitis C virus (HCV)
- Active infection requiring intravenous (IV) anti-infective usage within the last 7 days prior to study treatment
- Pregnant or breast-feeding
- Treatment with any investigational product within 28 days prior to Screening

4.3. Discontinuation of Subjects

4.3.1. Procedures for Withdrawal

Any subject may be removed from study for the following reasons:

- Subject withdrawal of the informed consent
- Subject noncompliance
- An increasing or unexpected pattern of unacceptable toxicity
- Disease progression
- Investigator judgment when the well-being and best interest of the subject is compromised

Subjects experiencing unacceptable toxicity should be removed from the study once complete resolution of toxicity has been documented. Individual subjects may be discontinued from the study by the investigator or sponsor at any time if either determines that it is not in the best interest of the subject to continue.

Any subject who becomes pregnant during the study must be discontinued from the study immediately, but should be followed through delivery or termination of the pregnancy. Subjects should also notify the investigator if they become pregnant within 28 days following the last dose of study drug. FPHU/Westat also must be notified if a subject becomes pregnant on study.

If a subject is discontinued from the study before completing the specified duration of treatment, they should be encouraged to complete the end-of-study assessments and to agree to report any serious adverse events for 28 days following the last dose of study drug. The date the subject is withdrawn and the primary reason for discontinuation will be recorded on the case report form (CRF).

4.3.2. Replacement of Study Subjects

Subjects who are screened, but do not receive FF-10501-01 will be replaced.

5. STUDY TREATMENT

5.1. FF-10501-01 Investigational Product Description

FF-10501-01 is an oral antimetabolite anticancer drug. It is a competitive inhibitor of IMPDH.

FF-10501-01 is a white powder provided in the form of film-coated immediate release tablets. In addition to FF-10501-01, formulation components include lactose monohydrate, light anhydrous silicic acid, carmellose calcium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, talc, and carnauba wax. FF-10501-01 is manufactured for FPHU by Patheon (Missisauga, Ontario, Canada) and will be provided by the sponsor (FPHU).

5.2. Study Drug Administration

FF-10501-01 will be provided directly from the drug distribution center designated by FPHU.

Subjects should be scheduled to begin study therapy following completion of Screening. FF-10501-01 will be administered orally at the dose level prescribed per cohort twice each

day **(approximately every 12 hours)**. For subjects on the 21-day dosing schedule, treatment will be continuous for 21 days for each 28-day cycle (=1 cycle). See **Appendix A** for drug dispensing guidelines.

A sufficient supply of FF-10501-01 will be dispensed to the subject by the investigator or trained designee for the subject to take on an outpatient basis between visits.

The following instructions should be reviewed with the subject and a written copy of the instructions provided to the subject:

- Take the prescribed dose of FF-10501-01 tablets (either 50 mg or 200 mg or both) by mouth twice each day with the second dose about 12 hours after the first dose.
- Take the tablets with a full glass of water (approximately 8 ounces). Swallow the tablets whole. Tablets should be taken in the fasting state, approximately 2 hours before or 2 hours after a meal.
- Your dose may be reduced if you have side effects. If a dose reduction is required, follow the instructions given by your doctor. Do not reduce the dose unless your doctor tells you to do so.
- If a scheduled dose of study drug is missed and less than 6 hours have passed since the scheduled dosing time, immediately take the missed dose. If more than 6 hours have passed since the scheduled dosing time, do not take the missed dose. Wait and take the next regularly scheduled dose.
- Each day record the number and dosage of tablets taken on the diary card. If a dose is missed, include the reason the dose was not taken.
- Return the diary card to your study doctor at each visit.
- Return opened and unopened bottles in which the tablets were dispensed.
- Adherence with the study treatment regimen must be assessed at each visit by checking the returned drug supply and reviewing the diary card. Study drug therapy must be reported in the appropriate case report form (CRF) module.

5.3. Treatment Duration

Treatment will continue until confirmation of disease progression, unacceptable toxicity, or subject decision to discontinue therapy

5.4. Dosing Delays and Dose Modifications Due to Toxicity

5.4.1. Toxicity Grading Criteria

Toxicity grading is based on NCI Common Terminology Criteria for Adverse Event v 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

5.4.2. Instructions Regarding Dose Delays and Dose Modifications

Adverse events considered for treatment interruption and dose reduction will exclude the events assessed by the investigator as exclusively related to underlying disease or medical

condition/concomitant treatment. If treatment must be delayed for reasons other than toxicity, contact the Medical Monitor to discuss the reasons for delay and plans for resuming study therapy.

- Treatment may be delayed up to 14 days. If the subject has completed two cycles and, in the investigator's opinion, is receiving benefit, treatment may be delayed for longer than 14 days and then resumed following a discussion with the Medical Monitor.
- Subjects who experience a toxicity requiring reduction in dose level may continue treatment at the lower dose level until disease progression or unacceptable toxicity. Once the dose has been reduced it may not be escalated to the starting dose.
- See **Appendix B** for FF-10501-01 dose modification requirements.

5.5. Supportive Care Guidelines

- Medications may be administered for the management of symptoms associated with the administration of FF-10501-01, as required.
- Prophylactic pre-medication will not be used routinely. Adequate treatment for nausea and/or vomiting and diarrhea is permitted during Cycle 1. After Cycle 1, prophylaxis of nausea and/or vomiting and diarrhea is permitted.
- Granulocyte stimulating growth factors (e.g., G-CSF or GM-CSF) are not allowed during Cycle 1 except for the following situations (defined as DLTs): Grade 4 neutropenia lasting 7 days or more, or failure of the absolute neutrophil count (ANC) to recover to Grade 1 within 12 weeks. After Cycle 1, use of granulocyte growth factors are allowed for prophylaxis or management of neutropenia.
- Erythropoiesis-stimulating agents, transfusions, etc. are permitted for management of hematologic toxicities.

5.6. Prior and Concomitant Medications and Therapies

5.6.1. Permitted Medications

All medications and other treatments taken by subjects 4 weeks before and throughout the study period will be recorded in the CRF module. Any changes in documented, permitted concomitant medications being taken at the beginning of the clinical trial or added during the time the subject is participating in this study must be recorded in the CRF module.

5.6.2. Prohibited Therapy

Concurrent anti-tumor therapy of any kind or any other investigational agent is prohibited.

Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes are prohibited, with the exception of anti-microbials that are used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient. See **Appendix C** for a list of drugs that may cause QTc prolongation or induce Torsades de Pointes.

5.7. Packaging and Labeling

FF-10501-01 will be supplied in 50 and 200 mg tablets for oral dosing. The study drug will be packaged in bottles labeled with pill strength and other information as per local regulatory requirements.

5.8. Shipping and Storage

The drug product has been demonstrated to be stable when stored in the defined container closure, high density polyethylene (HDPE) bottles. FF-10501-01 should be stored at room temperature (20 – 25 °C).

5.9. Drug Accountability

The investigator must maintain accurate records of receipt of study drug, dispensing information, and the prompt return or destruction of unused supplies. A drug accountability log will be supplied to each clinical site for purposes of recording study drug dispensation for the study and will be monitored by sponsor personnel. If the site has an electronic study drug accountability form that is in keeping with institutional practice and the form collects the same information as the form supplied by the Sponsor, this form may be substituted for the Sponsor's drug accountability form.

Unused or expired FF-10501-01 tablets will be destroyed per institutional policy.

6. STUDY PROCEDURES

See Schedule of Study Procedures in **Appendix D**.

6.1. Screening Procedures

The following evaluation includes standard tests are to be performed within 28 days of study treatment to determine subject eligibility.

- Administration of informed consent
- Medical history, physical examination and vital signs
- ECOG Performance Status
- Height and weight
- The following lab tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Beta HCG for WCBP
- 12-lead ECG
- Review of concomitant medications
- Disease-specific assessment (BM aspirate)

6.2. Requirements During Treatment Cycle 1

6.2.1. Cycle 1, Day 1

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests:
  - Hematology, if not performed within the previous 24 hours
  - Serum chemistry, if not performed within the previous 24 hours
  - Urinalysis, if not performed within the previous 24 hours
- 12-lead ECG, pre-dose and approximately 3 hours post-dose (following morning dose only)
- Review of concomitant medications
- Assessment of adverse events
- For subjects on 21-day dosing schedules: Peripheral blood collection in heparin for PK and XMP assessments, pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose
- For subjects on 21-day dosing schedule: Dispense 21-day supply of FF-10501-01 study drug for Cycle 1
- Assessment for survival

6.2.2. Cycle 1, Day 8 (+/- 1 day)

- Vital signs
- The following lab tests:
  - Hematology
  - Serum chemistry
- Review of concomitant medications
- Assessment of adverse events
- Review subject medication diary for FF-10501-01 study drug
- Assessment for survival

6.2.3. Cycle 1, Day 15 (+/- 1 day)

- Vital signs
- The following lab tests:

- Hematology
- Serum chemistry

- 12-lead ECG, pre-dose and approximately 3 hours post-dose (following morning dose only)
- Review of concomitant medications
- Assessment of adverse events
- For subjects on 21-day dosing schedules: Peripheral blood collection in heparin for PK and XMP assessments, pre-dose (within 15 minutes prior to dosing), between 0.5-1 hr post-dose, and between 2-4 hr post-dose
- Assessment for survival

6.2.4. Cycle 1, Day 22 (+/- 1 day)

- Vital signs
- The following lab tests:
  - Hematology
  - Serum chemistry
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

6.2.5. End of Cycle 1 (Day 28 +/- 3 days)

- Bone marrow aspirate (unless peripheral blood absolute blast count is $\geq 5.0 \times 10^9$ cells/L)
- Disease Response Assessment
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

6.3. Requirements During Treatment Cycles After Cycle 1 (Cycles 2, 3, 4, etc.)

6.3.1. Day 1 (+/- 3 days, except for pre-dose procedures; ECG)

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight

- The following lab tests (within 3 days of each cycle):
  - Hematology
  - Serum chemistry
  - Urinalysis
- 12-lead ECG, pre-dose and approximately 3 hours post-dose (following morning dose only)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival
- For subjects on 21-day dosing schedule: Dispense 21-day supply of FF-10501-01 study drug for cycle

6.3.2. End of Cycle 3 and Every 2 Cycles Thereafter

- Bone marrow aspirate (unless peripheral blood absolute blast count is $\geq 5.0 \times 10^9$ cells/L)
- Review of concomitant medications
- Assessment of adverse events
- Disease Response Assessment
- Assessment for survival

6.4. At Relapse or Progression of Disease

- Bone marrow aspirate (unless peripheral blood absolute blast count is $\geq 5.0 \times 10^9$ cells/L)
- Review of concomitant medications
- Assessment of adverse events
- Disease Response Assessment
- Assessment for survival

6.5. End of Study (Safety Visit, 28 days ± 5 days after the last dose of study drug)

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests:
  - Hematology

- Serum chemistry
- Urinalysis

- 12-lead ECG
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

6.6. Long-term Follow-up

Long-term follow-up will consist of a clinic visit or telephone call to assess survival every 3 months for up to 6 months.

7. DESCRIPTION OF ASSESSMENTS

7.1. Safety Assessments

7.1.1. Adverse Event Definition

An adverse event (AE) includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring whether or not temporally associated with study drug administration and whether or not considered related to study drug. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings.

An AE does **not** include the following:

- Medical or surgical procedures, e.g., tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred
- Abnormal laboratory value, unless it is clinically significant
- Overdose of study drug or concomitant medication unaccompanied by signs/symptoms (If sign/symptoms occur, the final diagnosis should be recorded as an AE.)
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case (The medical condition that leads to the hospitalization is to be recorded as the AE.)
- A significant worsening of the disease under investigation which is captured as an efficacy parameter in this study and, thus, is not to be recorded as an AE.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that results in any of the following outcomes:

- Death
- Life-threatening, i.e., immediate risk of death from the event as it occurred; (This does not include an adverse event that, had it occurred in a more serious form, might have caused death.)
- Persistent or substantial disability/incapacitation
- Results in or prolongs an existing inpatient hospitalization
- Congenital anomaly/birth defect

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

7.1.3. Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the investigational therapy, but are not specifically mentioned as occurring with the investigational therapy.

7.1.4. Adverse Event Reporting Period

The adverse event reporting period begins from the date of the first dose of study drug to 28 days following the last dose of study drug.

7.1.5. Recording of Adverse Events

Each AE should be recorded in standard medical terminology on the AE CRF module. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Dates of

start (onset) and stop (recovery), action taken, and outcome will be recorded in the AE CRF module.

All clinically significant abnormal changes in laboratory parameters will be recorded as an AE on the AE module, with the following exceptions: clinically significant abnormal laboratory changes determined to be related to the study condition and concomitant conditions, e.g., diabetes, of which the investigator was previously aware and that have not worsened.

The investigator will evaluate all AEs with regard to maximum intensity and relationship to study drug, as follows.

7.1.5.1. Maximum Intensity

Maximum intensity should be assigned using one of the severity grades as outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0); if the AE is not specifically listed in CTCAE v4.03, use the following grades:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

7.1.5.2. Relationship to Study Drug

The degree of certainty with which an AE is attributed to study drug (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of the study drug and/or reactions of similar nature previously observed with study drug. Each AE will be assigned one of the following five categories:

- *Not related:* There is not a temporal relationship to the study drug (e.g., too early, too late), or there is a reasonable causal relationship to another drug, concurrent illness, or circumstance.
- *Unlikely related:* There is a temporal relationship to study drug, but there is not a reasonable causal relationship between the time of study drug administration and the AE (i.e., it is doubtful the AE is related to the study drug); could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- *Possibly related:* There is a reasonable temporal sequence from time of study drug administration (e.g., occurred in a time frame relevant to study drug dose); or for which the possibility of the study drug being the causative factor (e.g., existence of similar reports attributed to the study drug; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as

underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.

- *Probably related:* There is a reasonable temporal sequence from time of study drug administration; and for which the possibility of factors other than the study drug administration, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.
- *Definitely related:* Follows a clear temporal sequence from time of study drug administration; could not be possibly explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; follows a response pattern known to be associated with study drug administration.

7.1.6. Most Commonly Expected Adverse Events

The most commonly reported adverse events in a Phase 2 study of 165 subjects with hematologic malignancies at doses of 14 – 600 mg/m^2 BID were nausea (9%), anorexia (7%), rash (4%), vomiting (4%), abdominal discomfort (2%) and pruritis (1%). Changes in laboratory values were elevated ALT (10%), AST (9%), thrombocytopenia (5%), decreased hemoglobin (2%), neutropenia (2%) and decreased bilirubin (2%). All other adverse events were reported at incidences of 1% or less. Laboratory changes were reported as temporary, ≤ Grade 2, and reversible. For bone marrow changes, nadir was reached in 2 -3 weeks for neutropenia, 3 weeks for platelets and 5 weeks for hemoglobin. Recovery from nadir values was approximately 2 weeks for all parameters.[7]

7.1.7. Adverse Event Reporting

Each AE is to be reported by the investigator as serious or non-serious according to the definitions in **Section 7.1.2** above. This classification determines the regulatory reporting procedures to be followed as described in **Table 6**.

Table 6. Reporting Guidelines for Adverse Events

Gravity of AE	Reporting Time to FPHU/Westat	Type of Report
Serious	Within 24 hours after the site becomes aware of the event	Initial SAE Report
Non-Serious	Per AE CRF module	Completed AE CRF Module

Any SAE, regardless of relationship to investigational therapy that occurs within 28 days following the last dose of study drug must be reported to the Medical Monitor within 24 hours after the site becomes aware of the event. The investigator is encouraged to discuss with the Medical Monitor any adverse experiences for which the issue of reportability is unclear or questioned. The initial report should be followed by submission of a more detailed SAE Report when follow-up information is available.

If the SAE occurs more than 28 days after the last dose of study drug, SAEs should be reported **only if considered related to FF-10501-01**. In the event of subject death, the reason for death should be recorded as the SAE, with 'death' recorded as the outcome on the SAE CRF module.

The SAE also will be recorded as an AE on the AE CRF module. Note: the SAE Report is different from the AE CRF. In areas of both forms where the same data are reported, the forms will be completed in a consistent manner. For example, the same term should be used for the AE on both forms, with the same start and stop dates, action taken, outcome, etc. A checkbox on the AE CRF module for whether the AE resulted in an SAE, will link the two types of report for a given event.

An SAE Report should be prepared with as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. If causality cannot be determined definitively at the time of the SAE occurrence, it is important to notify FPHU/Westat within the timeline stated above, and to attribute the relationship as 'Not Assessable' (only applicable for the initial SAE Report). When new significant information is obtained and the outcome and attribution of the event is known, the investigator will communicate this in a follow-up SAE Report. This relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by FPHU/Westat should be provided in a timely manner.

As necessary, the SAE Report should be accompanied by relevant pages from the CRFs, e.g., medical history, AEs, concomitant medications. Additional information may be requested by FPHU/Westat in an expedited manner to ensure that the initial reporting of the SAE made to the regulatory authorities complies with the required time frame. FPHU/Westat may be required to collect and report additional information to the regulatory authorities in a follow-up report, containing a final evaluation of the event, including copies of hospital reports, autopsy reports, or other relevant information.

7.1.8. Adverse Event and Serious Adverse Event Follow-Up

All AEs and SAEs should be followed until resolution, return to baseline, or until the point it is deemed that further recovery is unlikely. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and AE CRF module.

7.1.9. Ongoing Safety Evaluation

A study safety evaluation will be conducted on a regular (monthly) basis by teleconference. Dose exposure, dose-limiting toxicity, AE/SAE profiles and clinical laboratory abnormalities, and other safety measures will be reviewed during each convened meeting. Subject accrual will not be interrupted during the regular scheduled safety evaluations. These discussions will be led by the FPHU Medical Monitor and clinical site investigators.

7.1.10. Clinical Laboratory Tests

Clinical laboratory tests include hematology, serum chemistry, urinalysis and bone marrow aspirate (**Table 7**).

Table 7. Clinical Laboratory Parameters

Hematology	Serum Chemistry	Urinalysis	Bone Marrow Aspirate
Red blood cell count	Serum creatinine	pH	Marrow blast percent
Hemoglobin	BUN	Blood	Marrow cellularity percent
Hematocrit	Glucose (non-fasting)	Nitrites	Cell line maturation
White blood cell count	Albumin	Glucose	Auer rods
Differential:	AST	Ketones	Dysplasia
Neutrophils	ALT	Leucocytes	Cytogenetic abnormalities
ANC	LDH	Protein	
Lymphocytes	Total bilirubin	Microscopic examination	
Monocytes	Total protein		
Eosinophils	Alkaline phosphatase		
Basophils	Calcium		
Platelets	Phosphorus		
Blasts percent	Magnesium		
	Sodium		
	Potassium		
	Chloride		
	Bicarbonate		

7.1.11. Vital Sign Measurements

Vital sign measurements include blood pressure and pulse rate. Additional measurements may be obtained if clinically indicated. Any value considered clinically significant by the investigator will be recorded as an AE on the CRF. Clinically significant changes compared to baseline values should be followed until clinical resolution.

7.1.12. Physical Examinations

Complete physical examinations include the following body system evaluations: General Appearance, Skin, Musculo-skeletal, Eyes, Ears, Nose, Throat, Cardiovascular, Chest, Abdomen, Lymph Nodes, and Neurological.

Symptom-oriented evaluations will be performed when clinically indicated. Weight will be measured at Screening, Day 1 of each treatment cycle and the End of Study Visit.

7.1.13. Electrocardiograms

12-Lead ECGs will be performed at Screening, Cycle 1, Days 1 and 15, Day 1 of each subsequent cycle, and at End of Study.

7.2. Efficacy Assessments

7.2.1. Criteria for Evaluation of Response and Progression

Evaluation of response to treatment and determination of disease progression in subjects with AML will be evaluated using criteria defined in Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.[36] Efficacy assessments for subjects with MDS or CMML will be assessed using the modified International Working Group Response Criteria in Myelodysplasia.[37]

7.2.2. Disease Response Criteria

7.2.2.1. Subjects with AML

- **Complete Remission (CR)**

  The subject must be free of all symptoms related to leukemia and have an absolute neutrophil count > 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L, and normal bone marrow with < 5% blasts and no Auer rods

- **Complete Remission with Incomplete Blood Count Recovery (CRi)**

  As per CR but with residual thrombocytopenia (platelet count < 100 x 10^9/L) or residual neutropenia (absolute neutrophil count < 1.0 x 10^9/L)

- **Partial Remission (PR)**

  A ≥ 50% decrease in bone marrow blasts to 5 to 25% abnormal cells in the marrow; or CR with ≤ 5% blasts if Auer rods are present

- **Treatment Failure**

  Treatment has failed to achieve CR, CRi, or PR.

- **Recurrence**

  Relapse after confirmed CR: reappearance of leukemic blasts in peripheral blood or ≥ 5% blasts in the bone marrow not attributable in the Investigator's opinion to any other cause (e.g., bone marrow regeneration after consolidation therapy) or appearance of new dysplastic changes

7.2.2.2. Subjects with MDS or CMML

- **Complete Remission (CR)**
  The subject must be free of all symptoms related to leukemia and have an absolute neutrophil count ≥ 1.0 x 10^9/L, platelet count ≥ 100 x 10^9/L, bone marrow ≤ 5% myeloblasts, with normal maturation of all cell lines, hemoglobin ≥ 11g/dL, and no blasts in the peripheral blood

- **Partial Remission (PR)**

All CR criteria with ≥50% decrease in bone marrow blasts over pre-treatment (but still > 5%)

- **Marrow CR**
  In bone marrow, ≤ 5% myeloblasts and decrease by ≥ 50% over pre-treatment
- **Hematologic Improvement (HI) (subjects with MDS only)**
  - **Erythroid Response (HI-E)**
    - **Major Response**
      - ◊ For subjects with pretreatment hemoglobin < 11 g/dL, > 2 g/dL increase in hemoglobin
      - ◊ For RBC transfusion-dependent subjects, transfusion independence
    - **Minor Response**
      - ◊ For subjects with pretreatment hemoglobin < 11 g/dL, 1 to 2 g/dL increase in hemoglobin
      - ◊ For RBC transfusion-dependent subjects, ≥ 50% decrease in transfusion requirements
  - **Platelet Response (HI-P)**
    - **Major Response**
      - ◊ For subjects with a pretreatment platelet count < 100 x 10^9/L, an absolute increase of ≥ 30 x 10^9/L
      - ◊ For platelet transfusion-dependent subjects, stabilization of platelet transfusion independence
    - **Minor Response**
      - ◊ For subjects with a pretreatment platelet count < 100 x 10^9/L, a ≥ 50% increase in platelet count with a net increase > 10 x 10^9/L but < 30 x 10^9/L
  - **Neutrophil Response (HI-N)**
    - **Major Response**
      - ◊ For absolute neutrophil count (ANC) < 1.5 x 10^9/L before therapy, ≥ 100% increase or an absolute increase of ≥ 0.5 x 10^9/L, whichever is greater
    - **Minor Response**

◊ For ANC < 1.5 x 10^9/L before therapy, ANC ≥ 100%, but absolute increase < 0.5 x 10^9/L

- **Progressive Disease**
  Subject did not achieve PR, CR or marrow CR or is otherwise a non-responder.
- **Relapse after CR or PR**
  One or more of the following:
  - Return to pretreatment bone marrow blast percentage
  - Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
  - Reduction in hemoglobin concentration by ≥ 2 g/dL or transfusion dependence.
- **Progression or Relapse after Hematologic Improvement**
  One or more of the following:
  - A ≥ 50% decrement from maximum response levels in granulocytes or platelets
  - A reduction in hemoglobin concentration by ≥ 2 g/dL
  - Transfusion

7.2.3. Efficacy Endpoints

7.2.3.1. Primary Efficacy Endpoint

To evaluate the proportion of subjects with objective response achieved within 3 cycles of treatment with FF-10501-01 (i.e., within 3 months) in subjects with relapsed/refractory AML or relapsed/refractory high-risk MDS or CMML.

- **Subjects with AML**

  Objective responses for subjects with AML include complete remission (CR), complete remission with incomplete blood count recovery (CRi) and partial remission (PR) as defined above.
- **Subjects with MDS**
  Objective responses for subjects with high-risk MDS include complete remission (CR), partial remission (PR), and marrow CR as defined above.
- **Subjects with CMML**
  Objective responses for subjects with CMML include complete remission (CR), partial remission (PR) and marrow CR as defined above.

7.2.3.2. Secondary Efficacy Endpoints

The proportion of subjects with MDS who have hematologic improvement in peripheral blood or bone marrow blast count at any time after initiation of treatment with FF-10501-

01. Hematologic improvement in blast count is defined as ≥ 50% reduction in peripheral blood or bone marrow blast count when compared with the baseline value.

Progression-Free Survival: length of time from the date of first administration of study drug to the first objective evidence of disease progression or death, whichever is earlier.

Overall Survival: length of time from the date of first administration of study drug to the date of death from any cause

7.2.4. Timing of Assessments to Determine Response

Disease assessments will be made at the end of Cycle 1 and Cycle 3 and every two cycles thereafter. Disease assessments may be made at other time points at the discretion of the Investigator.

7.2.5. Pharmacokinetic Endpoints

Mean plasma concentrations of FF-10501 will be determined at each time point. Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of FF-10501-01 at each dose level will not be possible. Limited pharmacokinetic analyses will be performed.

7.2.6. Pharmacodynamic (PD) Endpoint

XMP is an intermediate in purine metabolism. It is formed from inosine monophosphate via the action of IMPDH, and is converted to guanosine monophosphate (GMP) via the action of GMP synthase (see **Figure 1**). The mechanism of action of FF-10501-01, namely, inhibition of IMPDH, should be associated with a decrease in XMP. Therefore, as a measure of pharmacologic activity of FF-10501-01 and preliminary measure of efficacy, levels of XMP in peripheral blood cells will be assessed in this study.

8. STATISTICAL METHODOLOGY

8.1. Determination of Sample Size

Phase 1: The sample size reflects requirements associated with a 3+3 design. A total of 3 to 36 subjects are planned (3 to 6 subjects in each of 6 dose cohorts).

Phase 2: The sample size reflects an additional 20 MDS/CMML patients to be treated at the MTD.

8.2. Analysis Populations

The full analysis set (FAS) includes all subjects who are administered any fraction of a dose of study medication. For a particular measure, the per-protocol set (PPS) includes those subjects in the FAS who have a valid baseline and one or more post-treatment assessments for that measure of interest.

The FF-10501-01 PK population consists of all subjects in the FAS who complete all PK assessments.

The FF-10501-01 PD population consists of all subjects in the FAS who complete all PD assessments.

8.3. Statistical Analysis Methods

All data will be analyzed using Statistical Analysis System (SAS Version 9.3 or higher for Windows, SAS Institute, Cary, NC). Continuous variables will be summarized using number, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number and frequencies.

8.3.1. Safety Analyses

8.3.1.1. Adverse Events

All safety endpoints will be summarized using descriptive statistics and will be based on the FAS dataset.

All AEs will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA; Version 15.0 or higher). An AE will be considered a treatment emergent adverse event (TEAE) if the onset is after the first dose of study drug or if the condition was present at baseline but worsened after the first dose.

All AEs for each subject will be listed, including intensity grading, relationship to study drug, action taken and outcome. Subject listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided. Subject narratives will be provided for deaths, SAEs and other significant AEs. Summary tables will be prepared to examine TEAE severity and relationship to study treatment.

AE summaries will be produced separately for each dose cohort and overall, and each disease cohort by dose and overall. All summaries will show, by subject group, dose cohort and overall, the number and percentage of subjects experiencing at least 1 TEAE of each preferred term, arranged by system organ class, and the number of occurrences of the event. Separate summaries will be produced by relationship to study medication, by severity, and for those events with an incidence rate of at least 2% in any group or overall.

SAEs will be summarized in a similar manner; overall, by relationship to study medication, and by severity.

In addition to the above, summaries of the number and percentage of subjects discontinuing the study due to AEs and, due to death, will be presented.

8.3.1.2. Laboratory Data

Laboratory data will be listed by subject. Values above and below normal ranges will be indicated, and whether statistically significant. All laboratory values will be graded according to the NCI-CTCAE version 4.03 criteria. Laboratory data will be summarized by actual value and change from baseline using number of non-missing observations, mean standard deviation, median, minimum and maximum. In addition, shift tables and the incidence of Grade 3 or 4 laboratory values will be presented.

8.3.1.3. Vital Signs

Vital signs will be listed by subject. Values above and below normal ranges will be indicated as will clinical significance. Vital sign data will be summarized by actual value and change from baseline using number of non-missing observations, mean, standard deviation, median, minimum and maximum.

8.3.1.4. Other Safety Data

Data collected for physical examinations, ECGs and related measures will be listed.

8.3.2. Efficacy Analyses

8.3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects treated at the MTD in each disease cohort (AML, MDS or CMML) with objective response (OR) within 3 cycles of study drug (i.e., within 3 months). For subjects with AML, OR is CR, CRi, or PR, as defined above. For subjects with MDS or CMML, OR is CR, PR or marrow CR, as defined above. The proportion of subjects in each disease cohort treated at the MTD will be summarized, and 90% confidence intervals will be estimated.

8.3.2.2. Secondary Efficacy Endpoints

The proportion of MDS subjects with hematologic improvement in the peripheral blood or bone marrow as defined as ≥ 50% reduction in blast count when compared with the baseline value. The 90% confidence interval will be estimated and provided.

Progression-free survival and overall survival curves will be estimated at the MTD by disease cohort using Kaplan-Meier product limit estimates. Median and 90% confidence interval of time-to-event will be estimated. Progression-free survival will be calculated from the date of first dose of study drug to the date of first objective evidence of disease progression or death, whichever is earlier. Overall survival will be calculated from the date of first dose of study drug to the date of death due to any cause. Subjects who did not experience progression or death will be censored at the last follow-up time point.

8.3.3. Pharmacokinetic Endpoint Analysis

Mean plasma concentrations of FF-10501 and plasma M1 will be determined at each time point for evaluation of dose-linearity. Because a limited number of plasma concentrations will be determined, full determination of routine pharmacokinetic parameters may not be possible. In addition to mean plasma concentrations, as the data allow, additional pharmacokinetic analyses will be provided (trough levels, $t_{1/2}$, T_{max}, C_{max}, AUC, etc.)

8.3.4. Pharmacodynamic Endpoint Analysis

Change from baseline in XMP levels will be measured in blood samples collected from each subject during the study. Correlations between XMP and PK levels of FF-10501 will be made. Pharmacodynamic parameters will be summarized using descriptive statistics

including the number of subjects, mean, standard deviation, minimum, median, maximum, range, and coefficient of variation.

8.3.5. Other Summaries

Demographics and concomitant medications, including antibiotic usage, will be summarized using descriptive statistics. Medical history findings and protocol deviations will be listed but not summarized.

9. STUDY MANAGEMENT

9.1. Data Management

The investigator is responsible for completing and maintaining adequate and accurate source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, CRF worksheets, etc. Data for this study will be submitted electronically. Access to the database will be provided following a brief on-line training session. Each user will receive a unique username and password, which should not be shared. The investigator must sign the investigator's statement for each subject indicating that the data reported are accurate. See **Appendix E** for Ethical Standards to be followed during the study.

9.2. Monitoring

The Sponsor and Westat are responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of subjects, subject recruitment, subject compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

9.3. Audits and Inspections

The Sponsor, Westat, a regulatory authority, or an IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact FPHU/Westat immediately if contacted by a regulatory agency about an inspection at their site.

9.4. Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment requires changes to the informed consent form, which also must be submitted for IRB approval prior to administration to subjects. If any changes to the CRF are required, Westat will issue supplemental or revised CRF pages on behalf of the sponsor.

9.5. Record Keeping

9.5.1. Health Insurance Portability Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR. Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor. See **Appendix F** for Investigator Obligations.

9.5.2. Financial Disclosure

The investigator shall provide to the sponsor sufficient accurate financial information to allow the sponsor and Westat to submit complete and accurate financial certification or disclosure statements to the FDA. The investigator shall promptly update this information if any relevant changes occur in the course of the study or for one year following completion of the study.

9.5.3. Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. “Original” in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

9.5.4. Retention of Study Documents

Study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor.

The investigator must not destroy any study-related records without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss

or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor must be contacted to arrange alternative record storage options.

10. ADMINISTRATIVE STRUCTURE OF THE STUDY

Westat will be responsible for data management, statistical analyses, and clinical study report writing. Clinical monitors under the direction of Westat will be used to monitor the study. Clinical laboratory parameters will be assessed by local laboratories and results recorded in the CRF module.

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Appendix A. Number of Tablets to be Administered Per Dose Level

Dose Level 50 mg/m^2 BID

Body Surface Area (m^2)	Total mg each Dose	Number Tablets Each Dose (50 mg)	Number Tablets Each Dose (200 mg)
≤ 2.00	100	2	0
2.01 – 3.49	150	3	0
≥ 3.5	200	0	1

Dose Level 100 mg/m^2 BID

Body Surface Area (m^2)	Total mg each Dose	Number Tablets Each Dose (50 mg)	Number Tablets Each Dose (200 mg)
≤ 1.50	150	3	0
1.51 – 2.00	200	0	1
≥ 2.01	250	1	1

Dose Level 200 mg/m^2 BID

Body Surface Area (m^2)	Total mg each Dose	Number Tablets Each Dose (50 mg)	Number Tablets Each Dose (200 mg)
≤ 1.25	250	1	1
1.26 – 1.62	300	2	1
1.63 – 1.87	350	3	1
1.88 – 2.12	400	0	2
≥ 2.13	450	1	2

Dose Level 300 mg/m^2 BID

Body Surface Area (m^2)	Total mg each Dose	Number Tablets Each Dose (50 mg)	Number Tablets Each Dose (200 mg)
≤ 1.37	400	0	2
1.38 – 1.51	450	1	2
1.52 – 1.65	500	2	2
1.66 – 1.77	550	3	2
1.78 – 2.05	600	0	3
2.06 – 2.17	650	1	3
≥ 2.18	700	2	3

Dose Level 400 mg/m^2 BID

Body Surface Area (m^2)	Total mg each Dose	Number Tablets Each Dose (50 mg)	Number Tablets Each Dose (200 mg)
≤ 1.25	500	2	2
1.26 – 1.37	550	3	2
1.38 – 1.51	600	0	3
1.52 – 1.65	650	1	3
1.66 – 1.77	700	2	3
1.78 – 1.91	750	3	3
1.92 – 2.05	800	0	4
2.06 – 2.17	850	1	4
≥ 2.18	900	2	4

Appendix B. FF-10501-01 Dosing Delays and Dose Modifications

Toxicity CTCAE Grade	During a Course of Therapy	Dose Adjustment for Next Treatment, (mg/m^2) BID* (%)				
		50	**100**	**200**	**300**	**400**
Grade 1	Maintain dose level					
Grade 2						
-1st occurrence	Interrupt until resolved to Grade 0-1	50 (100%)	100 (100%)	200 (100%)	300 (100%)	400 (100%)
-2nd occurrence	Interrupt until resolved to Grade 0-1	-	50 (50%)	150 (75%)	225 (75%)	300 (75%)
-3rd occurrence	Interrupt until resolved to Grade 0-1	-	-	100 (50%)	150 (50%)	200 (50%)
-4th occurrence	Discontinue treatment permanently OR dose reduce (200 – 400 mg/m^2 BID dose groups only)	-	-	50 (25%)	75 (25%)	100 (25%)
Grade 3						
-1st occurrence	Interrupt until resolved to Grade 0-1	-	50 (50%)	150 (75%) 100 (50%)	225 (75%) 150 (50%)	300 (75%) 200 (50%)
-2nd occurrence	Interrupt until resolved to Grade 0-1	-	-	50 (25%)	75 (25%)	100 (25%)
-3rd occurrence	Discontinue treatment permanently OR dose reduce (200 – 400 mg/m^2 BID dose groups only)	-	-			
Grade 4						
-1st occurrence	Discontinue permanently, OR, if physician deems it to be in the subject's best interest to continue, interrupt and/or dose reduce until resolved to Grade 0-1 (200 – 400 mg/m^2 dose groups only)	-	-	100 (50%) 50 (25%)	150 (50%) 75 (25%)	200 (50%) 100 (25%)

*Round up calculated unit dose to next unit dose based on tablet dose strength

Appendix C. Drugs Known to Prolong QT Interval or Induce *Torsades de Pointes*

CredibleMeds Known QTDrug L

The last revision date: November 2, 2016

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anticancer	Cancer (leukemia)
Astemizole (Removed from Market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil (Removed from Market)	Vascor	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride (Removed from Market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn	Antiarrhythmic	Abnormal heart rhythm
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea	Nausea, vomiting

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's
Dronedarone	Multaq	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine	Halfan	Antimalarial	Malaria

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Ibogaine (Only on Non US Market)	None	Psychedelic	Narcotic, addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (Removed from Market)	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia
Mesoridazine (Removed from Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Antineoplastic Agent	Cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from Market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Abnormal heart rhythm
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ulane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (Removed from Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride,	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from Market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor	Septic shock
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anticancer	Cancer (thyroid)

Appendix D. Schedule of Study Procedures

Study Activity	Screening[a]	Treatment Cycle 1					Treatment Cycles after Cycle 1		Progression or Relapse	End of Study[o]	Long-Term Follow-Up[p]
		Day 1	Day 8[k]	Day 15[k]	Day 22[k]	End of Cycle 1[l]	Day 1[m]	End of Cycle 3[n]			
Signed ICD	X										
Medical history	X										
Physical examination	X	X[j]					X[j]			X	
Vital Signs	X	X	X	X	X		X			X	
ECOG Performance Status	X	X					X			X	
Height	X										
Weight	X	X					X			X	
Hematology[b]	X	X	X	X	X		X			X	
Serum chemistry[c]	X	X	X	X	X		X			X	
Urinalysis[d]	X	X					X			X	
Beta-hCG for WCBP	X										
12-lead ECG	X	X[e]		X[e]			X[e]			X	
Concomitant medications	X	Continuous									
Adverse Event assessment		Continuous									
Bone Marrow Aspirate[f]	X					X		X	X		
Disease Response Assessment[g]	X					X		X	X		
Peripheral blood for PK assessment[h]		X		X							
Peripheral blood for PD (XMP) assessment[h]		X		X							
Administration of FF-10501-01[i]		BID x 21 days					BID x 21 days				
Assessment of survival		X	X	X	X	X	X	X	X	X	X

[a] Screening to be performed within 28 days of Cycle 1, Day 1
[b] Hematology collected at Screening, Days 1, 8, 15 and 22 of Cycle 1, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Study. See **Table 7** for tests to be conducted at each time point.
[c] Serum chemistry collected at Screening, Days 1, 8, 15 and 22 of Cycle 1, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Study. See **Table 7** for tests to be conducted at each time point.
[d] Urinalysis collected at Screening, Day 1 of Cycle 1, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Study. See **Table 7** for tests to be conducted at each time point.
[e] ECGs performed pre-dose and approximately 3 hours post-dose (following morning dose only)
[f] Bone marrow aspirate required at Screening; at end of Cycles 1 and 3, every 2 cycles thereafter, and at relapse/progression, unless peripheral blood absolute count is ≥ 5.0×10^9 cells/L. See **Table 7** for tests to be conducted at each time point.
[g] Disease Response Assessment may include bone marrow assessment, hematology for blood counts, physical exam, etc.
[h] Subjects on the 21-day dosing schedules: Peripheral blood collected in heparin for PK and PD assessment at Cycle 1, Day 1 pre-dose (any time), between 0.5-1 hr post-dose, and between 2-4 hr post-dose, and Cycle 1 Day 15 pre-dose (within 15 min prior to dosing), 0.5-1 hr post-dose, and 2-4 hr post-dose.
[i] Subjects on 21-day schedule, dose BID daily x 21 days each 28-day cycle
[j] Abbreviated physical exam
[k] Day 8, 15, or 22 +/- 1 day, except for pre-dose procedures for the cycle (e.g., ECG)
[l] Day 28 +/- 3 days
[m] Day 1 +/- 3 days except, for pre-dose procedures for the cycle (e.g., ECG)
[n] And every 2 cycles thereafter
[o] End of Study (Safety) visit should be 28 days from last dose of study medication (+/- 5 days)
[p] Long-term follow-up for 6 months consists of clinic visits or telephone calls every 3 months to assess survival status

Appendix E. Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice (GCP), US 21 Code of Federal Regulations (CFR) Part 50, (Protection of Human Subjects), US 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The U.S. Food and Drug Administration (FDA) regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP and FDA regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records; electronic signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- FDA Guidance for Industry: Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring, August 2013
- FDA Guidance for IRBs, Clinical Investigators, and Sponsors, June 2010
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
- FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, December 2012
- Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, 1996

Copies of these materials are available from the sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- The potential benefits of the research justify the risks.

FPHU is the sponsor of the Investigational New Drug Application (IND). The sponsor, or designee, if regulatory obligations have been transferred, is responsible for the following:

- Selecting qualified investigators,
- Providing investigators with the information they need to properly conduct an investigation,
- Ensuring proper monitoring of the investigation,
- Ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- Maintaining the IND, and
- Ensuring that FDA and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

Appendix F. Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the subject informed consent form will be approved by the institutional review board (IRB) before enrollment of any subjects. The opinion of the IRB will be dated and given in writing. A copy of the letter of approval from the IRB and a copy of the approved informed consent form will be received by the sponsor prior to shipment of study medication supplies to the investigator.

The investigator will ensure that the IRB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The investigator will also ensure that no changes will be made to the protocol without IRB approval.

As a part of the IRB requirement for continuing review of approved research, the investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines and FDA regulations, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). A FDA Form 1572 will be collected, listing the principal investigator and sub-investigators involved in the study. Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Protection of Human Subjects (21 CFR Part 50)

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB-approved consent form and signed by the subject or the subject's legally authorized representative. The Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the investigator's files and made available to and FDA representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the sponsor for review. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within

5 working days. In this situation, the investigator may not administer any subsequent product to that subject until informed consent and IRB approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the investigator. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study. The signed and dated consent must be retained with the study records and a copy provided to each participant.

In situations where the participant is not legally competent to provide consent (i.e., mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the sponsor and by the investigator's IRB prior to the initiation of the study. The document must contain the eight basic elements of informed consent and may contain the six additional elements described in 21 CFR Part 50. The attached Declaration of Helsinki-provides further details regarding the specific requirements for informed consent. Every consent form must include the following eight elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the

subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the investigator's part concerning subject consent.

Institutional Review Board (IRB) Ethic Review Committee (ERC) Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of participants in the study. It is the responsibility of the investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the sponsor.

When the sponsor provides the investigator with a Safety Report, the investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the investigator will submit a final report to the IRB/ERC and to the sponsor, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths

Study Files

The investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

Patient Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the principal investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or sponsor personnel.

Investigational Product Accountability

The investigator or designee is responsible for accountability of the investigational product at the site. The investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The investigator should ensure that the investigational product is used only in accordance with the protocol.