FUJIFILM Pharmaceuticals U.S.A., Inc.

FF1050101US101

A Phase 1/2a, Dose-escalation Study of FF-10501-01 for the Treatment of Advanced Hematologic Malignancies

Statistical Analysis Plan

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Prepared By:
Ken Gerald & Judy Chen
Biostatisticians

Westat
5615 Kirby Drive, Suite 710
Houston, TX 77005

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1. Project Overview

1.1. Project Design

(Protocol Amendment #7). 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), myelodysplastic syndrome (MDS), and chronic myelomonocytic leukemia (CMML) will be included. 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 is 4 – 5 subjects per month.

During the study, a Safety Review Committee, consisting of the actively recruiting investigators, the Medical Monitor, and FUJIFILM Pharmaceuticals U.S.A., Inc. (FPHU), will review data from each cohort on an ongoing basis.

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.

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.

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. Details of the PK analysis will be outlined in a separate Pharmacokinetic Report Analysis Plan.

1.2. Objectives

1.2.1. Primary Objective

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

1.2.2. 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 xanthosine monophosphate (XMP) as a pharmacodynamic marker

1.3. Treatment(s)

1.3.1. Treatment Assignments

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 were 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).

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

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/mm3 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.

At the MTD of 400 mg/m^2 BID, the 28-day continuous schedule of administration resulted in a higher rate of adverse events with no additional efficacy versus the 21-day schedule. Therefore, the recommended Phase 2 dose (RP2D) and schedule was determined to be 400 mg/m^2 BID on a 21-day schedule of administration, repeated every 28 days.

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.

1.3.2. Selection and Timing of Doses

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/m2 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/m2 BID, will not be dose-reduced. Up to 48 subjects are planned for Phase 1.

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.

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.

1.4. Procedures

1.4.1. Subject Identification

Once study eligibility has been determined, a subject will be enrolled into the study and will be assigned a sequential Subject Identification number within each participating site. The identification number will consist of a 2-digit site number, 1-digit cohort number, and a 2 digit subject number. The subject identification number will be assigned sequentially within the cohort. The cohort number will remain the same if a subject's dose is increased or decreased. If a subject is replaced, the identification number will not be reassigned.

1.4.2. Randomization

Not Applicable

1.4.3. Blinding/Unblinding

This is an unblinded study.

1.4.4. Replacement

Subjects who are enrolled and are assigned a Subject Identification number but do not receive FF-10501-01 will be replaced.

1.4.5. Data Monitoring

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

The Sponsor is 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.

2. Statistical Analysis Considerations

2.1. Sample Size and Power

Up to 68 total subjects are planned in this study.

Phase 1: Up to 48 subjects are planned for Phase 1. The sample size reflects requirements associated with a 3+3 design. A total of 3 to 48 subjects are planned (3 to 6 subjects in up to 8 dose cohorts).

Phase 2a: The sample size reflects an additional 20 patients to be treated at the RP2D and schedule with CMML/MDS.

2.2. Analysis Populations

2.2.1. Full Analysis Set (FAS) Population

The full analysis set (FAS) includes all subjects who are administered any fraction of a dose of study medication

2.2.2. Randomized Population

Since this is not a randomized study, there is no randomized population.

2.2.3. Per Protocol Set (PPS) Population

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.

2.2.4. Safety Population

All safety endpoints will be based on the FAS dataset.

2.2.5. PK/PD Population

The FF-10501-1 PK population consists of all subjects in the FAS who complete at least one post-dose PK assessment. The PD population consists of all subjects in the FAS who complete at least one post-dose PD assessment.

2.3. Data Handling

2.3.1. Measurement Times

2.3.1.1. Visit Windows

Visit windows will not be used. The visit time point entered on the case report forms will be used. Unscheduled assessments, if any, will be listed, but will not be included in tabulations by visit.

2.3.1.2. Baseline Values

The screening assessments are performed within 28 days of Cycle 1, Day 1, before the first dose of study medication. Unless otherwise mentioned, baseline will be the last observation before patients receive initially assigned dose. Generally, this will be Cycle 1 Day 1 pre-dose measurements. If a pre-dose assessment is not performed on Cycle 1 Day 1, the immediate previous non-missing value, including screening, will be treated as baseline. If there are multiple baseline assessments, the most recent one will be flagged as the baseline value and will be used for statistical analysis (evaluations may occur on the same day as Study Day 1, prior to dosing).

2.3.2. Missing Data Conventions

Unless otherwise specified, missing data will be considered missing and will not be imputed.

2.3.3. Imputation of Incomplete Dates

Imputation of partial dates may be performed during the data analysis and will be documented. For start date of Adverse Event (AE) or Concomitant Medication (CM) with a missing day, the imputed date is the first day of the month. For stop date of AE or CM with a missing day, the imputed date is the last day of the month. For start date with both missing day and missing month, the imputed date is the subject start study date if AE or CM start year is the same as study start year. Otherwise, the imputed start date is the first day of the year. For stop date with both missing day and missing month, the imputed date is the subject end of study date if AE or CM stop year is the same as the study end year. Otherwise, the imputed stop date is the last day of the year.

2.4. Statistical Methods

2.4.1. General Overview and Plan of Analysis

All data will be analyzed using Statistical Analysis System (SAS Version 9.4 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 frequencies and percentages.

2.4.2. Hypothesis Testing

No formal hypothesis tests are planned.

2.4.3. Modeling

Not Applicable in this study.

2.4.4. Multiplicity Issues/Multiple Comparisons

There is no planned Multiplicity Issues/Multiple Comparisons analysis for this study.

2.4.5. Project Center Effects

The study will be conducted at The University of Texas M.D. Anderson Cancer Center (Guillermo Garcia-Manero, M.D.), Study Chair and Case Comprehensive Cancer Center (Mikkael Sekeres, M.D.). Other sites may be added to ensure timely accrual to the study.

2.4.6. Interim Analysis

No formal interim analysis is planned. AE listings and appropriate summary tables will be generated for Scientific Review Committee meetings and Development Safety Update Reports (DSURs).

2.4.7. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic and Pharmacodynamic data will be summarized in a separate report.

3. Statistical Analysis

Data will be presented for clinical review and interpretation. Categorical variables will be summarized using frequency counts and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum). All listings will be presented for the FAS population except for PK and PD data.

3.1. Enrollment and Disposition of Subjects

Enrolled individuals are referred to as “subjects”. Subjects with acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and chronic myelomonocytic leukemia (CMML) will be included.

Major selection criteria are: age ≥ 18 years, confirmed high risk MDS/CMML or AML with documented disease progression following previous therapy, or subjects with AML ≥ 60 years of age who are not candidates for other therapies. 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.

The analyses of subject disposition will be performed on the FAS population for subjects in Phase 1 dose escalation phase by dose cohort and for subjects in Phase 2a phase by MDS/CMML disease cohort. The number and percentage of subjects will be presented. The number of subjects treated, and treated subjects who completed follow-up and those who terminated early from treatment and the study, along with their reasons for early termination, will be presented.

3.2. Baseline Characteristics

3.2.1. Demographic

Summary statistics for demographic characteristics will be presented for subjects in Phase 1 dose escalation phase by dose cohort and for subjects in Phase 2a phase by MDS/CMML disease cohort using the full analysis set (FAS) population. Tabulations will be performed for age, sex (male or female), ethnicity (Hispanic/Latino or other), and race (American Indian or Alaska Native, Black or African American, White, Asian, Native Hawaiian or Other Pacific Islander, Unknown, or other). Age will be calculated as the number of complete years between a subject’s date of birth and the date of screening visit.

3.2.2. Physical Characteristics

Summary statistics will be presented for height (cm) and weight (kg) at screening for subjects in phase 1 by dose cohort and for subjects in phase 2a by disease cohort treated at RP2D using the FAS population. ECOG performance status at screening will be summarized.

3.2.3. Disease Characteristics

The baseline disease assessment (AML and MDS/CMML) will be summarized for phase 1 subjects by dose cohort and for phase 2a subjects treated at RP2D and schedule using the FAS population.

3.2.4. Concomitant Medications at Entry

Concomitant medications coded using WHO Drug Dictionary will be summarized using descriptive statistics for phase 1 subjects by dose cohort and for phase 2a subjects by MDS/CMML disease cohort using the FAS population. Medication start and stop dates will be compared to the date of first dose of medication to allow medications to be classified as either Prior or Concomitant. Medications that start and stop prior to the date of first dose of study medication will be classified as Prior medications. If a medication starts before the date of first dose of study medication or starts on or after the first dose of study medication, and

stops on or after the date of first dose of study medication, then the medication will be classified as Concomitant.

3.3. Analysis of Efficacy

All efficacy analyses will be conducted for Phase 1 subjects by dose cohort, if applicable, and for Phase 2a subjects by MDS/CMML disease cohort at the RP2D and schedule (400 mg/m^2 BID x 21 days, repeated every 28 days) using the Per Protocol Population (PPS dataset).

3.3.1. Primary Endpoints

The primary efficacy endpoint is 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.

3.3.2. Secondary 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.

3.3.3. Exploratory/Other Analyses

Pharmacokinetic and pharmacodynamic analyses will be provided by an outside laboratory.

3.4. Analysis of Safety and Tolerability

3.4.1. Study Drug Administration

Overall duration of exposure, dose intensity, and relative dose intensity will be summarized using descriptive statistics by dose cohort for Phase 1 subjects and by MDS/CMML disease cohort for Phase 2a subjects. Duration of exposure to study drug in each cycle will be calculated as the date of last dose minus the date of first dose plus one if there are no drug interruptions. For drug interruptions, the number of days in each cycle will be calculated as date of last dose minus the date of first dose plus one times the actual dose taken (in mg) divided by the dose prescribed (in mg) during the cycle. The number of days in all such cycles will be added within each dose cohort to calculate overall duration. The total dose taken will be calculated based on the actual dose information collected in the CRF. Dose intensity will be calculated as the total dose divided by the number of scheduled days on drug. Relative dose intensity will be calculated by dividing the dose intensity by starting dose.

3.4.2. Adverse Events

All safety endpoints will be summarized using descriptive statistics and will be by dose cohort for phase 1 subjects and by MDS/CMML disease cohort for phase 2a subjects treated at RP2D and schedule using the FAS population.

All AEs will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA; Version 17.0 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 other AEs will be considered preexisting events.

All AEs for each subject will be listed, including Treatment Emergent status, intensity grading, relationship to study drug, action taken and outcome. Subject listings of deaths, serious TEAEs, and TEAEs leading to treatment discontinuation will be provided. Summary tables will be prepared to examine TEAE severity and relationship to study treatment.

TEAE summaries will be produced separately for each dose cohort for subjects in Phase 1 and by MDS/CMML disease cohort for subjects in Phase 2a. All TEAE summaries will show the number and percentage of subjects experiencing at least 1 TEAE for each preferred term, arranged by system organ class, and the number of unique occurrences of the event. Separate summaries will be produced by relationship to study medication, and by severity, and for those events with an incidence of at least 2% in any group or overall. Subjects with multiple events will be counted only once per SOC and preferred term. For each level of summarization, the event with the highest level of severity, grade, or strongest drug relationship will be presented. TEAEs with Grade 3 or Grade 4 and drug-related TEAES with Grade 3 or Grade 4 will be summarized. TEAEs leading to study drug interruption or discontinuation, Grade 3 and 4 TEAEs, Serious TEAEs will be provided in a separate listing.

3.4.3. Clinical Laboratory Results

Laboratory data will be listed by subject. Values above and below normal ranges will be indicated. 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, maximum, and Grade 3 and 4 by dose cohort and by disease cohort treated at RP2D and schedule. In addition, shift tables will be presented.

3.4.4. Vital Signs

Vital signs will be listed by subject. 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 by dose cohort for Phase 1 subjects and by MDS/CMML disease cohort for Phase 2a subjects treated at RP2D and schedule.

3.4.5. Physical/Other Examinations

Data collected for physical examinations, ECGs and related measures will be listed. ECGs change from baseline will be summarized by dose cohort for Phase 1 subjects and by MDS/CMML disease cohort for Phase 2a subjects.

3.4.6. Treatment Discontinuation, Project Termination, and Death

The participants who discontinued (with reasons) and deaths will be listed. The treatment emergent adverse events leading to permanent discontinuation from study will be presented.

4. Proposed Summary Tables, Graphs and Listings

4.1. Mock Tables

The following tables will be presented by dose cohort for subjects in Phase 1 dose escalation phase, and by disease cohort for subjects in Phase 2a.

4.1.1. Subject Disposition

- Subject Disposition

4.1.2. Demographics and Baseline Characteristics

- Demographics and Baseline Characteristics (Ethnic, Race, Sex, Age at Study Entry, Weight, Height and ECOG)
- Baseline Disease Assessment - AML
- Baseline Disease Assessment - MDS/CMML

4.1.3. Prior and Concomitant Medication

- Summary of Prior Medications
- Summary of Concomitant Medications

4.1.4. Primary Efficacy Summaries

- Summary of Subject's Disease Response and 90% Confidence Intervals - AML
- Summary of Subject's Disease Response and 90% Confidence Intervals - MDS/CMML

4.1.5.Secondary Efficacy Summaries

- Summary of Subjects With Hematologic Improvement
- Progression Free Survival (PFS)
- Overall Survival (OS)

4.1.6. Safety Summaries

4.1.6.1. Study Drug Administration

- Summary of Study Drug Exposure

4.1.6.2. Adverse Events Summaries

- Summary of Treatment Emergent Adverse Events

- Treatment Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment Emergent Adverse Events by Relationship to Study Drug
- Summary of Treatment Emergent Adverse Events by Severity
- Grade 3 and Grade 4 Treatment Emergent Adverse Events
- Drug-related Grade 3 and Grade 4 Treatment Emergent Adverse Events
- Treatment Emergent Adverse Events by System Organ Class and Preferred Term with at least 2% Incidence in any Group or overall

4.1.6.3. Laboratory Assessments

- Summary of Laboratory Assessments by Visit
- Change From Baseline in Laboratory Assessments by Visit
- Shift Table from Baseline to Most Extreme Post-Baseline Result by CTC Grade

4.1.6.4. Other Safety Summaries

- Summary of Vital Sign Results
- Change From Baseline in Vital Sign Results
- Change From Baseline in 12-Lead Electrocardiogram Results

4.2. Mock Graphs

- Progression Free Survival
- Overall Survival

4.3. Mock Listings

The following listings will be presented for subjects in Phase 1 dose escalation phase and for subjects in Phase 2a.

- Inclusion Criteria not Met
- Exclusion Criteria not Met
- Protocol Violations/Deviations/Exemptions
- Demographics
- End of Treatment
- End of Study
- Baseline Disease Assessment - AML
- Baseline Disease Assessment - MDS/CMML
- Medical History
- Prior Cancer Surgery
- Physical Examination
- Prior Medications
- Concomitant Medications
- Study Drug Administration - Drug Dispensation
- Study Drug Administration – Patient Medication Diary
- Pharmacokinetic (PK) Sample Collection
- Pharmacodynamic (PD) Sample Collection

- Disease Response - AML
- Disease Response - MDS/CMML
- Bone Marrow Assessment (BMA)
- Treatment Emergent Adverse Events (TEAE)
- Serious Treatment Emergent Adverse Events
- Treatment Emergent Adverse Events Leading to Dose Adjustment, Temporary Interruption, and Permanent Discontinuation of Study Drug
- Treatment Emergent Adverse Events Leading to Permanent Discontinuation from Study
- Dose Limiting Toxicities
- Deaths
- Hematology
- Chemistry
- Urinalysis
- Pregnancy Test
- Vital Signs
- 12-lead Electrocardiogram
- Blood Transfusion
- Other Procedures
- Long Term Follow-up