Protocol ARO-009

Phase II Study of Crenolanib Besylate Maintenance following Allogeneic Stem Cell Transplantation in Patients with FLT3-positive Acute Myelogenous Leukemia

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TITLE:
Phase II Study of Crenolanib Besylate Maintenance following Allogeneic Stem Cell Transplantation in Patients with FLT3-positive Acute Myelogenous Leukemia

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1. SYNOPSIS

Name of Investigational Product
Crenolanib besylate (AR-868,596-26)

Title of Study
Phase II Study of Crenolanib Besylate Maintenance following Allogeneic Stem Cell Transplantation in Patients with FLT3-positive Acute Myelogenous Leukemia

Number of Planned Patients
48 patients

Length of Study
2 years

Primary Objective

- To assess progression-free survival (PFS) time, defined as the time to disease progression or death, whichever occurs first, starting when crenolanib administration is begun.

Secondary Objectives

- To assess disease-free survival (DFS) time, overall survival (OS) time, graft-versus-host disease, and 100-day transplant-related mortality.

Study Rationale

The treatment of FLT3-mutant AML is complicated by the poor outcome with standard induction and consolidation therapy. To date the use of allogeneic transplant in first remission is of limited effectiveness to improving outcomes due to persistent relapse risks. Crenolanib is a FLT3 targeted TKI that has preliminary clinical activity as a salvage therapy in a heavily pretreated AML population with FLT3 ITD, FLT3 D835, and compound FLT3 ITD/D835 mutations including those with resistance after prior TKI therapy. Given the favorable safety profile of crenolanib and promising clinical benefit in AML patients, a trial examining the role of crenolanib as maintenance in the post-transplant setting is warranted.

Crenolanib besylate is an orally bioavailable benzimidazole that was designed to be a selective and potent inhibitor of the class III receptor kinase FLT3. Molecular binding data support that crenolanib is a type I kinase inhibitor that binds preferentially to the active kinase conformation of FLT3. As a result of this property, crenolanib potently inhibits both wild type and constitutively active mutant FLT3 kinase. Specifically, in 51 patients with relapsed/refractory FLT3 ITD and/or TKD mutant AML including relapse following multiple lines of therapy including prior TKIs, crenolanib was well tolerated and demonstrated an overall clinical benefit of 55% including complete remission (CR), incomplete hematological recovery (CRi), and partial remission (PR). Six of 51 patients of this heavily pretreated group were bridged to transplant.

Study Design
This is a study of crenolanib as maintenance in the post-HSCT setting in AML patients with FLT3 mutations.

Forty-eight patients who have undergone first allogeneic transplant eligible to receive oral crenolanib besylate will be enrolled. There will be two cohorts in the study. Cohort A will include patients who underwent allogeneic SCT while in first or second complete remission with count recovery. Cohort B will include patients who underwent HSCT with incomplete count recovery although they had ≤%10 bone marrow blasts at the time of HSCT.

Start of maintenance crenolanib therapy is intended at the earliest time no sooner than 42 days but no later than 90 days after allogeneic HSCT.

Maintenance therapy with crenolanib will be given at a dose of 100 mg BID. Patients considered at high risk of relapse, i.e. patients in second remission after prior relapsed or refractory disease, patients with measurable residual disease, or patients who received a haploidentical HSCT may receive 100 mg TID.

Crenolanib should be taken at least 30 minutes prior to or following a meal. Patients will complete a daily diary for 728 days to record the date, time, and amount (number of tablets) of crenolanib taken and relation to eating schedule (Appendix III).

Patients may take crenolanib continuously for up to 728 days or until one of the criteria for study discontinuation is fulfilled. Cycles of therapy will be repeated every 28 days, and therapy will be continued until clinically significant disease progression or documentation of unacceptable toxicity as determined by the investigator or 728 days of therapy are reached. If the drug is discontinued for toxicity, patient should be reassessed until toxicity has resolved.

Patients who have discontinued study drug for reasons other than toxicity will be followed for 30 days post last dose or until the commencement of new therapy, whichever occurs earlier.

Inclusion Criteria

1. History of AML according to WHO classification
2. First allogeneic HSCT using MAC, NMA or RIC preparative regimens.
3. FLT3-ITD or FLT3-D835 positive disease at any time during disease course.
4. Hematopoietic stem cell source is either with peripheral blood, bone marrow or cord blood.
5. Donor source is matched related, unrelated, haploidentical donor or cord blood.
6. At the time of allogeneic HSCT:
   a. No more than 1 antigen mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 locus for unrelated donor with peripheral blood and bone marrow as the hematopoietic stem cell source; and
   b. Bone marrow blast ≤ 10%
7. No sooner than 42 days but no later than 90 days after allogeneic HSCT.
8. Post-transplant bone marrow blast count ≤ 5% confirmed within 21 days (+4 days) prior to starting study therapy
9. Evidence of donor engraftment as defined by institutional standard T cell chimerism> 50%.

10. Adequate engraftment within 7 days prior to starting study therapy: ANC ≥ 1.0 x 10^9/L without daily use of myeloid growth factor; and platelet ≥ 25 x 10^9/L without platelet transfusion within 1 week
11. Non-hematological toxicities ≤ Grade 2
12. Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
13. Adequate liver function within 24 hours of start of crenolanib administration:
    - with serum AST ≤ 2 x ULN and ALT ≤ 2 x ULN
    - and bilirubin within the normal range
14. Acute GVHD ≤ Grade 1, either no signs of chronic GVHD or mild chronic GVHD graded as limited disease
15. ECOG performance status of 0-2
16. Age ≥ 18 years with the capacity to give written informed consent
17. Non-pregnant and non-nursing women of childbearing potential must have a negative serum or urine pregnancy test ("Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months)
18. Women of childbearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation and for 90 days following completion of therapy

Exclusion Criteria

1. Bone marrow blast >5% within 21 days (+ 4 days) of start of study drug
2. Active GVHD grade ≥2
3. Concurrent use of corticosteroids equivalent of prednisone at a dose > 0.5 mg/kg
4. Active and/or untreated central nervous system (CNS) leukemia
5. Concomitant therapies for treatment or control of leukemia
6. Use of any of the following after transplantation and prior to starting study therapy:
   a. Chemotherapeutic agents for therapy of AML (note that prophylactic use of these agents is allowed in this study, e.g., methotrexate for GVHD)
   b. Investigational agents/therapies
   c. Azacitidine, decitabine or other demethylating agents
   d. Lenalidomide, thalidomide and pomalidomide
7. Uncontrolled infection
8. Known positive for HIV; active HBV or HCV infection
9. Significant cardiac disease (New York Heart Association classes III or IV) or unstable angina despite medication
10. Pregnant or breast-feeding
11. Major surgery within 4 weeks of starting study drug
12. Receipt of investigational agents within 5 half-lives of last dose of investigational agent
13. Prior treatment with crenolanib with progression on treatment

Statistical Methods

Preliminaries
This is a single-arm, Phase II study of crenolanib in allogeneic stem cell transplant in patients with acute myeloid leukemia (AML) in CR after allogeneic stem cell transplantation. Administration of crenolanib is oral, and will be started at some time between 42 and 90 days post-transplant, and then given every day for up to two years. There are two patient subgroups: 1) those that were in complete remission (CR) at the time of transplant, and 2) those that were not in complete remission (NCR) at the time of transplant. The primary outcome is progression-free survival (PFS) time, defined as the time to disease progression or death, whichever occurs first, starting when crenolanib administration is begun. A maximum of 24 patients will be enrolled in each subgroup.

Futility Monitoring
PFS time will be monitored separately within each of the two subgroups, using the Bayesian method of Thall et al. [1]. Denote standard therapy by S and the experimental crenolanib therapy by E. Assume that TS = PFS time with S follows an exponential distribution with median mS and that TE = PFS time with E in the each subgroup follows an exponential distribution with median mE. Denote the median PFS times for the standard and experimental therapies by mS and mE, respectively. Under a Bayesian model, both mS and mE are assumed to follow Inverse Gamma(a, b) priors.

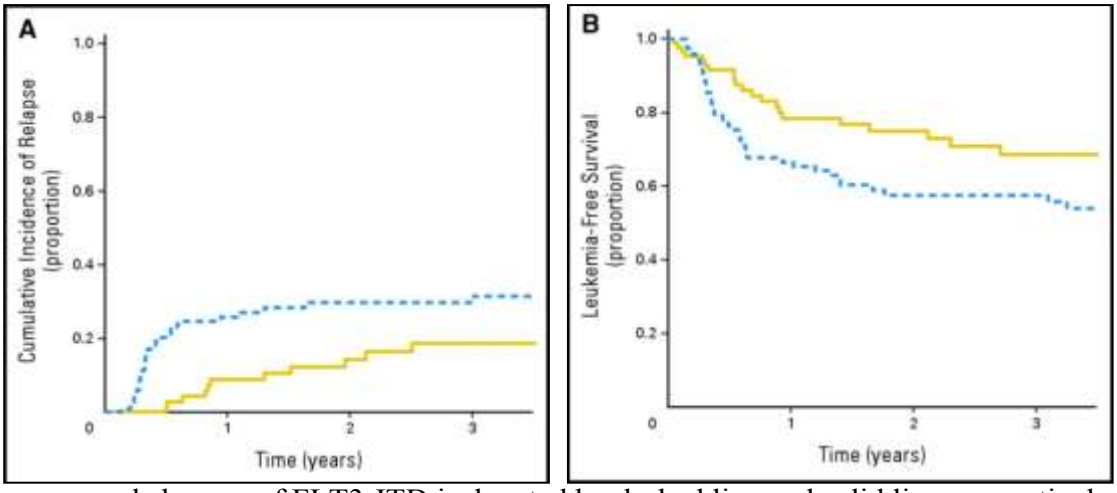
Secondary outcomes and data analyses.
Secondary outcomes will include disease-free survival (DFS) time, overall survival (OS) time, graft-versus-host disease, and 100-day transplant-related mortality. Within each subgroup, CR and no CR, these events will be tabulated and the distributions of DFS and OS time estimated using the method of Kaplan and Meier [2].

2. BACKGROUND AND STUDY RATIONALE

2.1 Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is offered to eligible patients with suitable donor to increase long term survival in patients with FLT3 positive acute myelogenous leukemia (AML). However, disease relapse due to presence of minimal residual disease (MRD) remains a key reason of treatment failure in post-transplant patients [1]. Furthermore, a recent study showed that the presence of internal tandem duplication of FLT3 gene (FLT3-ITD) correlated with a higher risk of relapse and lower leukemia free survival (LFS) after allogeneic HSCT performed in first CR (Figure 1.1).

Figure 2.1 *FLT3*-ITD – A Negative Prognostic Marker After Allogeneic HSCT in 1st CR [2]



Presence and absence of FLT3-ITD is denoted by dashed line and solid line, respectively. (A) Estimated probability of 2 years of cumulative incidence of relapse; (B) leukemia-free survival after transplantation at 2 years.

The majority of relapses occur within 8 months after transplant [3] and most patients who relapse after allogeneic HSCT do not achieve long-term survival with available salvage treatment modalities including second HSCT. Prophylactic donor lymphocyte infusion (DLI) has been used to prevent relapse of AML in the post-transplant setting; however, it is often associated with life-threatening GVHD [4]. Therefore, it is critical to develop a novel agent which can be given when minimal MRD is present, is tolerable, has activity against the disease, and can be given early after transplant.

2.2 Crenolanib inhibits wild-type FLT3 and constitutively active mutations

Crenolanib, a FMS like tyrosine kinase inhibitor (TKI), is well tolerated in relapsed/refractory FLT3 mutant positive AML patients after allogeneic HSCT and may present a novel pathway to prevent relapse.

Crenolanib besylate (also known as CP-868,596-26) is an orally bioavailable class III RTK inhibitor that potently targets FLT3. Crenolanib inhibits wild-type FLT3 and its constitutively active mutations at clinically achievable concentrations.[5, 6]

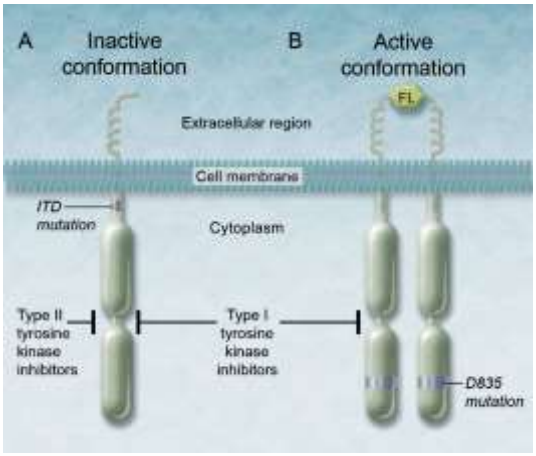
Crenolanib has heightened binding affinity against the FLT3-ITD mutation (the most frequent FLT3 aberration in AML) and TKD point mutations FLT3 (D835H), FLT3 (D835Y) and FLT3 (D835V). Crenolanib binds to FLT3-ITD and FT3-TKD D835H with Kd values of 0.43 and 0.4 nM, respectively. Similarly, crenolanib also binds to FLT3-TKD D835Y with a Kd of 0.18 nM. A saturation mutagenesis screen of FLT3 ITD showed that crenolanib is a "pan-FLT3 inhibitor" that has the ability to successfully suppress all resistance-conferring TKD mutants[5]. Crenolanib inhibitory activity has been verified in human AML cell lines. [5]

Table 2.1 Dissociation constants of crenolanib with constitutively active FLT3 mutations

Gene Symbol	Crenolanib K_d (nM)
FLT3(ITD)	0.43
FLT3(D835H)	0.4
FLT3(D835Y)	0.18
FLT3 (D835V)	0.048

Crenolanib is a type 1 tyrosine kinase inhibitor that is active against FLT3 regardless of conformation status.

Figure 2.2 Schematic of inactive and active FLT3 with most common resistance mutations in AML.[7]



Crenolanib has reduced activity against KIT

Crenolanib has been found to be approximately 100-fold more selective for FLT3 than for KIT and is therefore highly selective toward FLT3 relative to KIT [8] and elicits cytotoxicity in FLT3–mutant AML while largely sparing KIT inhibition (100-fold offset in both viability and

biochemical assays) with limited activity against other kinases. As a result, crenolanib may be associated with less myelosuppression than the other FLT3 TKIs.

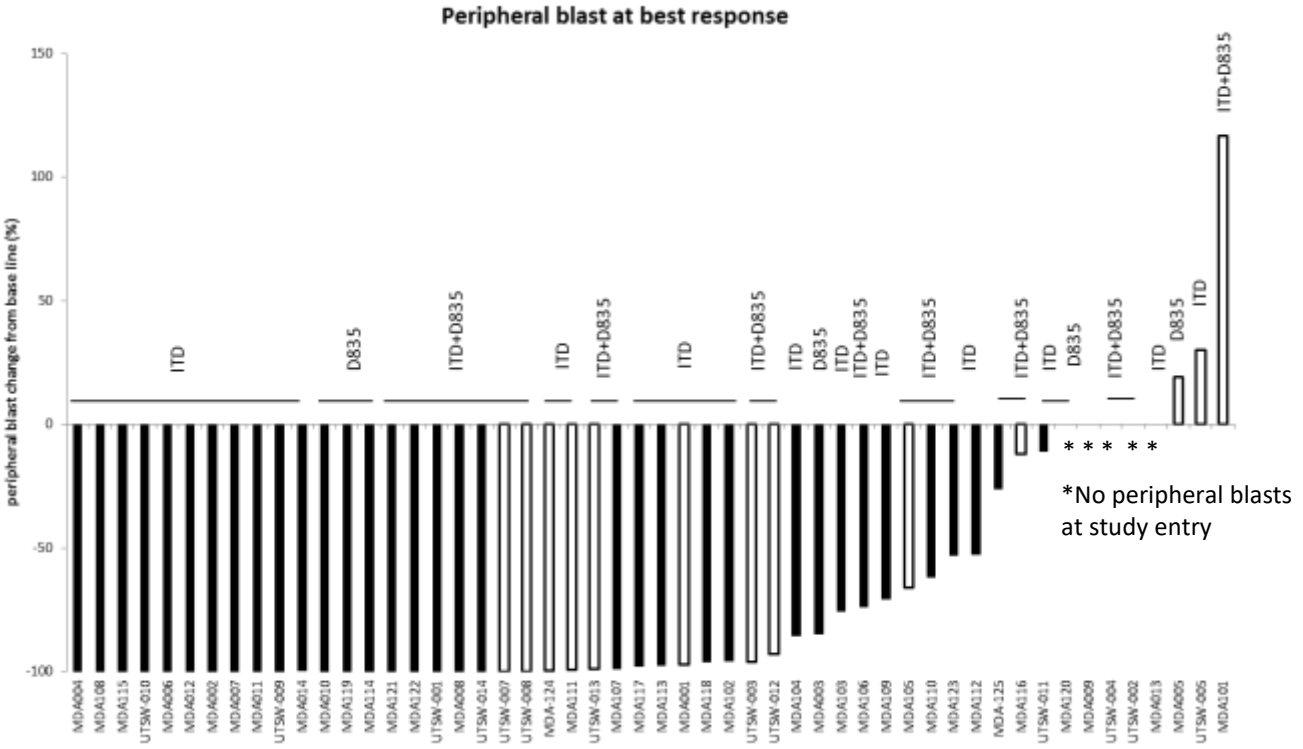
2.3 Clinical Studies of Crenolanib in AML

2.3.1 Clinical Summary of Crenolanib in Relapsed/Refractory FLT3 mutated AML

Crenolanib has been studied in relapsed/refractory FLT3 mutant AML (NCT01522469, NCT01657682). As of July 30, 2014, a total of 51 AML patients have been treated with single-agent crenolanib. Patients had received a median number of 3 prior therapies for AML (range 1-7) including prior transplant and TKI therapy.

Of the 51 AML patients (FLT3 ITD, or FLT3 D835, or FLT3 ITD/D835) treated with crenolanib, 49 patients were eligible for efficacy evaluation. Crenolanib has demonstrated clinical activity in this heavily treated population. Several patients showed peripheral blast clearance after crenolanib therapy (Figure 5.5). Twenty-seven (27) patients have demonstrated response, including 1 complete remission (CR) with full count recovery, 8 CR with incomplete hematological recovery (CRi), 7 partial remissions (PR) and 11 blast responses. Clinical benefit rate was 55 %. Five (11 %) of these heavily pre-treated patients were bridged to transplant. Of the 25 patients with FLT3-D835 AMl, 14 patients have gained clinical benefit (56 %): 6 CR/CRi (24%), 4 PR (16 %), and 4 blast response (16 %) [9, 10].

Figure 2.3 Peripheral blast clearance in FLT3 mutant AML patients treated with crenolanib.



Toxicity data from 38 patients is available. Overall, crenolanib was well-tolerated. Commonly observed side effects included nausea (76 %), vomiting (52 %), diarrhea (47%), and transaminase

elevations (8-11 %). Two patients went off study due to toxicities, one due to nausea/ vomiting and one due to fatigue. Dose reduction occurred in 2 patients, one due to nausea and another due to transaminitis, respectively.

As of yet, QT prolongation has not been reported in the 51 patients with AML treated with crenolanib. Most patients had received concomitant medication including antifungal medicine throughout crenolanib therapy; nonetheless no QT prolongation has been observed.

In conclusion, crenolanib is a FLT3 TKI that has showing preliminary clinical activity in a heavily pretreated AML population with FLT3-ITD, FLT3-D835, and compound FLT3-ITD/D835 mutant disease. Importantly, crenolanib is the first agent to demonstrate clinical activity in patients with FLT3-D835 activating mutations.

2.3.2 Tolerability of Crenolanib in AML Patients Who Have Undergone Prior Allogeneic Bone Marrow Transplant

Within the 51 AML patients treated with single agent crenolanib, a total of thirteen patients (6M, 7F) had undergone prior allogeneic stem cell transplants. Seven patients received crenolanib at a dose of 100 mg TID (total daily dose of 300 mg). Six patients received a higher total daily dose of 200mg/m^2/day given in three divided doses.

The median age of these patients was of 55 years (37-76). The median duration between allogeneic HSCT and initiation of crenolanib therapy was 249 days (34-1313). Nine patients had progressed after prior FLT3 TKI exposure (7 patients had had prior treatment with sorafenib, 4 with midostaurin, 3 with quizartinib, and one with PLX3397).

Overall, a similar rate and spectrum of toxicities were observed when crenolanib was administered at either dose level to these 13 previously transplanted patients as compared to the non-transplanted patients with relapsed AML. The most common adverse events were gastrointestinal (nausea (31%), vomiting (31%), diarrhea (23%), and constipation (23%)), and infections (pneumonia (23%), mucositis oral (21%), and fever (15%)).

Three of the six patients who received the higher total dose of 200mg/m^2/day of crenolanib required dose reduction due to toxicities: one patient for periorbital edema, one patient for neutropenia, and another patient for elevated bilirubin. This latter patient was found to have reactivation of GVHD on liver biopsy as major causative factor causing elevated bilirubin. The patient with neutropenia recovered his neutrophil counts after stopping valganciclovir. The patient with periorbital edema was able to resume crenolanib without recurrence of the edema. All seven patients treated with the 100 mg TID dose of crenolanib tolerated drug well without needing a dose reduction. None of these 7 patients was discontinued for toxicities. Therefore, it appears crenolanib at 100 mg TID should be reasonably tolerated in this patient population.

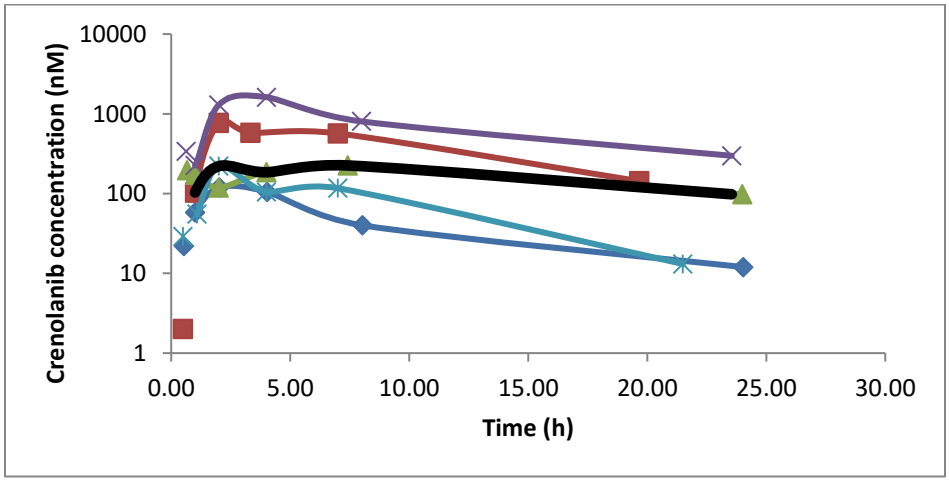
2.3.3 Long-term Safety Data of Crenolanib

Crenolanib has been given to patients with relapsed FLT3(+) AML for up to five months without any cumulative toxicities. In a Phase I pediatric glioma study conducted at the St. Jude Children's Research Hospital, 6 children received crenolanib for at least 12 months and two children stayed on study drug for 24 months. Long-term exposure to crenolanib seems to be tolerable and safe.

2.4 Rationale for Baseline Dose Selection

Day 1 pharmacokinetics data is shown in Figure 5.7 for 7 post-HSCT patients receiving a 100 mg TID dose of crenolanib. The crenolanib pharmacokinetics did not appear to be altered in patients who had had prior HSCT (as compared to the other AML patients). However, due to the vulnerability of this patient population, out of abundant caution, crenolanib will be administered at a dose of 100 mg BID. Patients considered at high risk of relapse, i.e. patients in second remission after prior relapsed or refractory disease, patients with measurable residual disease, or patients who received a haploidentical HSCT may receive 100 mg TID.

Figure 2.4 Crenolanib pharmacokinetics in AML patients with a prior history of HSCT (dose 100mg TID)



Patients with post-allo BMT receive immunosuppressive agents including tacrolimus. These agents are typically tapered off by Day 100 post-transplant. A number of other anti-microbial agents are also gradually tapered off post 100 days of allogeneic transplant. As this protocol allows patients to start as early as Day 42, patients earlier in the transplant course will be started at 60mg BID. Dose will be escalated no sooner than at 1 month intervals to 80 mg BID, then to 80 mg TID. That dose will then be maintained for a maximum of 2 years maintenance.

Rationale for this trial

The treatment of FLT3-mutant AML is complicated by the poor outcomes with standard induction and consolidation therapy. To date the use of allogeneic stem cell transplantation in first remission is of limited effectiveness to improving outcomes due to persistent relapse risks. Crenolanib is a FLT3 targeted TKI that has preliminary clinical activity as a salvage therapy in a heavily

pretreated AML population with FLT3 ITD, FLT3 D835, and compound FLT3 ITD/D835 mutations including those with resistance after prior TKI therapy. Given the favorable safety profile of crenolanib and promising clinical benefit in AML patients, a trial examining the role of crenolanib as maintenance in the post-transplant setting is warranted.

3. STUDY OBJECTIVES

Primary Objective

- To assess progression-free survival (PFS) time, defined as the time to disease progression or death, whichever occurs first, starting when crenolanib administration is begun.

Secondary Objectives

- To assess disease-free survival (DFS) time, overall survival (OS) time, graft-versus-host disease, and 100-day transplant-related mortality.

4. STUDY DESIGN

This is a phase II study of crenolanib as maintenance in the post-HSCT setting in AML patients with FLT3 mutations.

Forty-eight patients who have undergone first allogeneic transplant eligible to receive oral crenolanib besylate will be enrolled. There will be two cohorts in the study. Cohort A will include patients who underwent allogeneic SCT while in first or second complete remission with count recovery. Cohort B will include patients who underwent HSCT with incomplete count recovery although they had ≤%10 bone marrow blasts at the time of HSCT.
Start of maintenance crenolanib therapy is intended at the earliest time no sooner than 42 days but no later than 90 days after allogeneic HSCT.

Maintenance therapy with crenolanib will be given at a dose of 100 mg BID. Patients considered at high risk of relapse, i.e. patients in second remission after prior relapsed or refractory disease, patients with measurable residual disease, or patients who received a haploidentical HSCT may receive 100 mg TID.

Crenolanib should be taken at least 30 minutes prior to or following a meal. Patients will complete a daily diary to record the date, time, and amount (number of tablets) of crenolanib taken and relation to eating schedule (Appendix III).

Patients may take crenolanib continuously for up to 728 days or until one of the criteria for study discontinuation is fulfilled. Cycles of therapy will be repeated every 28 days, and therapy will be continued until clinically significant disease progression or documentation of unacceptable toxicity as determined by the investigator or 728 days of therapy is reached. If the drug is discontinued for toxicity, patient should be reassessed until toxicity has resolved.

Patients who have discontinued study drug for reasons other than toxicity will be followed for 30 days post last dose or until the commencement of new therapy, whichever occurs earlier.

5. PATIENT SELECTION

Patients must have baseline evaluations performed within 7 days (except otherwise specified) prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

5.1 Inclusion Criteria

1. History of AML according to World Health Organization (WHO) classification
2. First allogeneic hematopoietic stem cell transplantation (HSCT) using myeloablative conditioning (MAC), non-myeloablative (NMA), or reduced-intensity conditioning (RIC) preparative regimens.
3. FLT3-ITD or FLT3-D835 positive disease at any time during disease course.
4. Hematopoietic stem cell source is either with peripheral blood, bone marrow or cord blood.
5. Donor source is matched related, unrelated, haploidentical donor or cord blood.
6. At the time of allogeneic HSCT:
   a. No more than 1 antigen mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 locus for unrelated donor with peripheral blood and bone marrow as the hematopoietic stem cell source; and
   b. Bone marrow blast ≤ 10%
7. No sooner than 42 days but no later than 90 days after allogeneic HSCT.
8. Post-transplant bone marrow blast count ≤ 5% confirmed within 21 days (+4 days) prior to starting study therapy
9. Evidence of donor engraftment as defined by institutional standard T cell chimerism > 50%.
10. Adequate engraftment within 7 days prior to starting study therapy: ANC ≥ 1.0 x 10^9/L without daily use of myeloid growth factor; and platelet ≥ 25 x 10^9/L without platelet transfusion within 1 week
11. Non-hematological toxicities ≤ Grade 2
12. Serum creatinine ≤ 1.5 × ULN OR creatinine clearance ≥ 50mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal
13. Adequate liver function within 24 hours of start of crenolanib administration:
    a. with serum AST ≤ 2 x ULN and ALT ≤ 2 x ULN
    b. and bilirubin within the normal range
14. Acute graft-versus-host disease (GVHD) ≤ Grade 1, either no signs of chronic GVHD or mild chronic GVHD graded as limited disease
15. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
16. Age ≥ 18 years with the capacity to give written informed consent
17. Non-pregnant and non-nursing women of childbearing potential must have a negative serum or urine pregnancy test ("Women of childbearing potential" is defined as a

sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months)

18. Women of childbearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation and for 90 days following completion of therapy

5.2 Exclusion Criteria

1. Bone marrow blast > 5% within 21 days (+4 days) of start of study drug
2. Active GVHD grade ≥ 2
3. Concurrent use of corticosteroids equivalent of prednisone at a dose > 0.5 mg/kg
4. Active and/or untreated central nervous system (CNS) leukemia
5. Concomitant therapies for treatment or control of leukemia.
6. Use of any of the following after transplantation and prior to starting study therapy:
   a. Chemotherapeutic agents for therapy of AML (note that prophylactic use of these agents is allowed in this study, e.g., methotrexate for GVHD)
   b. Investigational agents/therapies
   c. Azacitidine, decitabine or other demethylating agents
   d. Lenalidomide, thalidomide and pomalidomide
7. Uncontrolled infection
8. Known positive for human immunodeficiency virus (HIV); active hepatitis B (HBV) or hepatitis C (HCV) infection
9. Significant cardiac disease (New York Heart Association classes III or IV) or unstable angina despite medication
10. Pregnant or breast-feeding
11. Major surgery within 4 weeks of starting drug
12. Receipt of investigational agents within 5 half-lives of last dose of investigational agent
13. Prior treatment with crenolanib with progression on treatment

6. TREATMENT PLAN

After providing informed consent, subjects fulfilling the eligibility criteria will be enrolled in the study. The Sponsor should be provided the complete "Enrollment Checklist" indicating the request to enroll the patient to the trial. After review, the Sponsor will provide the site a "Confirmation of Enrollment" signifying enrollment of the patient to the trial and formal verification of the study unique patient identifier number (UPIN).

Baseline Screening

The following assessments will be performed after completion of the informed consent and within 7 days of start of study drug except as otherwise specified (Appendix IV):

1. Medical history, Demographics and physical exam
2. Height, weight, and vital signs
3. ECOG Performance Status
4. Serum or urine pregnancy test for women of child bearing capacity

5. CBC, platelet count, and differential
6. Chemistry panel* including creatinine, total bilirubin, ALT, and AST
7. HIV, hepatitis B, and hepatitis C screening (unless previously tested for prior to HSCT)
8. Concomitant medications review
9. Evaluation of baseline adverse events

* Liver function tests including ALT, AST, and bilirubin need to be re-checked within 24 hours at the commencement of crenolanib. ALT and AST must be ≤ 2 x ULN and bilirubin must be normal.

The following assessments will be performed within 21 days (+4 days) of start of study drug except as otherwise specified:

1. Bone marrow aspirate (BMA) to assess remission status, FLT3 testing and a portion for correlative testing (see Section 9.0).
2. Evaluation of FLT3-D835, FLT3-ITD and other mutational status at the time of HSCT.

6.1 Evaluation during Treatment

During crenolanib maintenance, the following will be evaluated (Appendix IV):
("Cycle" will be defined as 28 consecutive days regardless of whether crenolanib is ingested or not. Assessments should be done approximately 28 days apart).

Protocol assessments start as of Day 1 (D1) of cycle 1. D1 correlates with start of study drug.
As specified, on-therapy laboratory assessments may be done with a local non-1572 MD with results available for PI but patient must be evaluated at the study center at least once weekly until three months following transplant, and once per return visit to the study site/institution following this. Return visits to the study site/institution will be at least once a month for the first 6 months and then every 3 months for the rest of the maintenance therapy.

The investigator is responsible for ensuring that all information required per protocol has been obtained, reviewed, and recorded on CRFs per study protocol.

1. ECOG, vital signs, and weight q28days (± 7 days). ECOG assessment by phone interview is allowable after the first six cycles; during the last 18 cycles, VS and weight may be taken by local non-1572 physician and data provided to study center for investigator review per protocol stipulated timeframes.
2. CBC with platelet count and differential must be obtained D1 (+ 2 days) and D14 (±7 days) during the first 14 days of maintenance then q28days (± 7 days). CBC per local non-1572 physician is allowed to be used for this assessment but must be reviewed by the study investigator within the protocol specified timeframe. Results are to be recorded in the CRF. CBC at the study site to be done no less than every 3 cycles.
3. Chemistry panel including creatinine, total bilirubin, ALT, AST must be obtained D1 (+ 2 days) and D14 (±7 days) then q28days (± 7 days). Labs per local non 1572 physician are allowed to be used for this assessment but must be reviewed by the study investigator within the protocol specified timeframe. Results are to be recorded in the CRF. Chemistry panel at the study site to be done no less than every 3 cycles.

4. Bone marrow at loss of CR or if at any time during therapy a bone-marrow sample is obtained for clinical purposes, a portion of the sample is requested to also be sent to Propath (Appendix XI).
5. Serum or urine pregnancy test for women of child bearing capacity should be done every 3 cycles while on study.
6. Peripheral blood for correlative studies as per Study Calendar (Appendix IV) *
7. Concomitant medications are to be reviewed at each study visit during the first two cycles and thereafter per cycle ± 7 days. An interview by telephone is allowed to obtain this information. Data are to be recorded in study CRFs
8. Adverse event evaluation weekly during first 14 days then q28days ±7 days. Telephone interview assessment to obtain information is allowed but must be done within protocol specified timeframe. Data is to be recorded in study CRFs. Patient should be assessed at the study site for adverse events considered of significance or possibly study drug related.
9. Patient will have contact information of their treating physician and PIs of the study to reach them anytime while they are treated by their local non-1572 MD.

*Every effort will be made to collect correlative studies at defined time points for all patients; however, missing collection in one or more of these time points in occasional patients will not be considered a protocol deviation/violation.

6.2 Evaluation during Follow-up

All patients who do not discontinue study drug for toxicity will need to be followed for 30 days post-discontinuation to address any late developing toxicities which may occur. This follow up will cease when patients start a new therapy if prior to the 30-day follow up interval.

To assess secondary end points of PFS and overall survival, all patients will need to be followed till relapse, progression and death.

STUDY THERAPY

6.3 Crenolanib Maintenance Therapy

Generally, patients will be treated according to the following:

- Maintenance therapy with crenolanib is intended in all patients in CR/CRi after allogeneic HSCT.
- Start of maintenance crenolanib therapy is intended at the earliest time no sooner than 42 days but no later than 90 days after allogeneic HSCT.
- Prerequisites for start of maintenance are hematological recovery with neutrophils >1.0 x 10^9/L, all non-hematological toxicities have to be below CTCAE grade 2, GVHD ≤ Grade 1, either no signs of chronic GVHD or mild chronic GVHD graded as limited disease.
- Maintenance therapy will be given for up to 728 days. (up to 26 cycles where 1 cycle of therapy is defined as 28 consecutive days regardless of whether study drug is taken or not) after recovery from allogeneic HSCT as long as the patient does not develop disease progression while on crenolanib therapy.
- Patients should take their doses at approximately the same time each day, and approximately 8 hours should elapse between doses. Each dose should be given at least 30 minutes prior to

or 30 minutes after food with a glass of water (no juice) (~240 ml). Patients should be instructed to swallow the tablets whole and not to chew them.

- Maintenance therapy with crenolanib will be given at a dose of 100 mg BID. Patients considered at high risk of relapse, i.e. patients in second remission after prior relapsed or refractory disease, patients with measurable residual disease, or patients who received a haploidentical HSCT may receive 100 mg TID.
- Dose reduction guidelines for adverse events are listed in Table 7.1 and 7.2 in Section 7.1. Dose reductions beyond those mentioned in these tables or different than those specified, should be discussed with the Sponsor and documentation of the justification recorded.
- Antiemetics per ASCO guidelines for moderately emetogenic therapy should be instituted. Reduction in antiemetic support can be individualized as appropriate.
- If a dose is missed or vomited, it should not be taken again. The next dose should not be increased to account for missing a dose. The patient should note the missed dose in the patient diary and take the next regular dose at the regularly scheduled time.
- Subsequent cycles may be delayed for recovery of toxicity. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only after determination of the principal investigator of potential risk/benefit ratio.
- For patients who discontinue therapy, the reason for treatment discontinuation will be captured.

6.4 Duration of Therapy

Treatment may continue for 728 days until one of the following criteria applies:

1. progressive disease defined as:
   1.1 Death due to any cause
   1.2 Start of any non-protocol therapy directed toward AML
   1.3 Relapse defined as detection of leukemia blasts in the peripheral blood OR >5% blasts in marrow not attributed to another cause.
2. Intercurrent illness that in the opinion of the investigator prevents further administration of treatment, or
3. Patient request, or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy, or

It is planned that up to a total of 728 days of therapy will be administered for patients deriving benefit from this regimen.

A minimum of 1 full course (defined as the administration of crenolanib for 28 days) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. Only those patients who failed to complete at least one cycle (28 consecutive days) of crenolanib therapy, unless they progressed or dropped out due to toxicity will be replaced. All patients receiving at least one dose of study drug will be considered evaluable for toxicity.

7. DOSING AND DOSE MODIFICATIONS OF CRENOLANIB

Toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

7.1 Dose Reductions of Crenolanib for Non-hematologic Toxicities

Dose reductions for non-hematologic toxicities due to crenolanib, will be done according to the schema outlined in Table 7.1 and 7.2. Dose levels are outlined in Table 7.3.

Table 7.1 Crenolanib dose reduction for all toxicities (except GI (nausea, vomiting and diarrhea)) related to study drug

Toxicity **(NCI Criteria)**	Dose Modification
Grade 1 or 2	No dose modification
Clinically significant persistent grade 2 despite optimal therapy	Hold drug until toxicity resolves to grade 1 or less. Restart drug at same dose level (Table 7.3).
Grade 3 or 4	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (Table 7.3).

Table 7.2 Crenolanib dose reduction GI toxicity related to study drug

Toxicity **(NCI Criteria)**	Dose Modification
Grade 1 or 2	No dose modification
Clinically significant persistent grade 2 or 3 despite optimal therapy	Hold drug until toxicity resolves to grade 1 or less. Restart drug at same dose level (Table 7.3).
Grade 4	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (Table 7.3).

7.2 Dose Reductions of Crenolanib for Hematologic Toxicities

It is expected that some patients who commence maintenance crenolanib will have abnormal baseline blood counts.

Patients who develop hematologic toxicities while on maintenance crenolanib should follow the dose modifications as outlined below:

- Patients with counts of neutrophils >1x10^9/L and platelets >100 x10^9/L should not have any dose modification.
- Patients with pre-cycle counts of neutrophils >1x10^9/L and platelets >100 x10^9/L and no evidence of residual leukemia who have sustained neutropenia <0.5 x10^9/L or platelet counts <25 x x10^9/L for more than 4 consecutive weeks in the current cycle, may receive a subsequent cycle at 1 dose level reduction. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest.

7.3 Dose Modifications of Crenolanib due to Toxicities

Dose Modifications of Crenolanib due to Toxicities

One dose reduction to 80 mg BID is allowed in a single subject for toxicity management regardless of the attribution. Reductions below 80 mg BID are not planned. Dose reductions beyond 80 mg BID or different form the dose specified below should be discussed with and approved by the sponsor or its designees. Any dose modification, including dose hold and dose delay, must be documented and justified in the eCRF. Dose re-escalation is in general not allowed on this study. Any exception must be approved by the sponsor in writing.

Table 7.3 Crenolanib dose reduction schedule

Dose level	Crenolanib dosing
0	100 mg BID
-1	80 mg BID

Patients considered at high risk of relapse, i.e. patients in second remission after prior relapsed or refractory disease, patients with measurable residual disease, or patients who received a haploidentical HSCT may receive 100 mg TID.

If more than 20% (more than 1 patient of the first 5 patients enrolled; more than 2 patients of the first 10 patients enrolled; or more than 3 patients of the first 15 patients enrolled) of the subjects require crenolanib dose reduction during the first 2 cycles of therapy, then the study will be paused for protocol re-evaluation. These data will be presented to the Sponsor's safety monitoring team to determine whether the crenolanib dose should be modified for all future patients.

7.4 Cycle Delays

- A cycle of therapy may be delayed to allow recovery from toxicities.
- Delays in start of subsequent cycles greater than 8 weeks will be acceptable only after determination of the principal investigator of the potential risk/benefit ratio.

7.5 Concomitant Medications

In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted. Other anticancer agents including systemic chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study.

Antiemetics per ASCO guidelines for moderately emetogenic therapy should be instituted. Reduction in antiemetic support can be individualized as appropriate.

No other investigational drugs are allowed during the study without consent of the medical monitor.

8. AGENT FORMULATION AND PROCUREMENT

Crenolanib is supplied as 20 mg tablets for oral dosing, in 30-count bottles. Crenolanib tablets should be refrigerated at a temperature between 2°C and 8°C (35.6°F and 46.4°F). Standard household refrigeration is considered adequate for drug storage. Crenolanib should be stored in the vials provided by the pharmacy and kept out of the reach of children.

Used bottles and unused tablets and bottles should be returned by the patient to the treating physician before starting a new therapeutic cycle to assess treatment compliance. Study drug will be supplied by AROG Pharmaceuticals, Inc. Study drug may be packaged by a third party. Clinical trial materials will be labeled according to regulatory and institutional requirements.

9. CORRELATIVE STUDIES

9.1 Pharmacokinetic Assay

Sample Collection

Samples collected during study of crenolanib therapy will be collected into no additives added (red top) vacutainers and will be transported to the laboratory.

Sampling Strategy

Peripheral blood for pharmacokinetic studies will be drawn pre- and post-administration of crenolanib dose at the following time points:
Cycle 1 Day 1: 120 (±15) minutes, 4 (±1) hours, 8 (±2) hours after crenolanib administration.
Cycle 2 Day 1: pre-dose and at 3 (±1) hours after crenolanib administration.
Cycle 3 Day 1: pre-dose and at 3 (±1) hours after crenolanib administration.

These samples should be labeled with time of sample relative to last dose of drug ingested.

Sampling Processing Instructions

The date and time of sample collection, crenolanib dose, and date and time of the last crenolanib dose should be recorded on the appropriate Pharmacokinetics Data Collection Form (Appendix VII-A, VIII-A and IX-A).

Sampling Handling and Shipping Instructions

In preparation of shipping samples, contact AROG Pharmaceuticals (refer to appendix XV) and MicroConstants (Appendix XI) to notify of sample shipment and to provide FedEx tracking number. Samples should be shipped within 60 days of the last sample collection. Specimens collected should be shipped via FedEx Priority Overnight shipping for delivery Tuesday through Thursday. Weekend and holiday deliveries should be avoided. Ship all pharmacokinetic samples on dry ice, along with a completed Pharmacokinetics Data Collection Forms.

9.2 Bone Marrow Samples

Sampling collection schedule:
During screening procedures (after obtaining informed consent), a portion of the enrollment (baseline) sample of bone marrow or peripheral blood containing blasts should be obtained. A **sample of this marrow should also be shipped on same day as collection as per instructions below.**

Samples from additional bone marrow aspirations obtained while the patient is on study should be submitted in a similar fashion.

Sampling Collection:
Bone marrow aspiration will be done as per institutional protocol which will be on day 100 ±10, 6^{th} month ± 1 month, 1^{st} year ±1 month and 2 years ±2 months after allogeneic stem cell transplantation. Patients may have repeat bone marrow evaluation any time when deemed necessary by the treating physician.

Shipping of bone marrow samples:
Bone marrow aspirates should be shipped to the laboratory promptly on the day of collection on wet ice along with a completed Data Collection Form (Appendix X) by overnight courier (FedEx).

In preparation of marrow sample shipment, contact AROG Pharmaceuticals and ProPath (Appendix XI) to notify of sample shipment and provide the FedEX tracking number.

9.3 Other tissue samples

Tissue cells and blood samples may be requested for assessment in other tests which assess study drug activity and will be banked for future correlative science research studies. Additional correlative science research may be performed at the discretion of the investigators or AROG, including assays for resistance studies for cases in which responses are noted but are not durable.

10. CRITERIA FOR RESPONSE MAINTENANCE

Response criteria will be modified from the International Working Group for AML (34). Patients on this trial should be in CR, CRi, or PR following allogeneic SCT with evidence of donor engraftment documented per institutional standard. Briefly, CR criteria and definition of progression are as follows:

Complete Remission (CR):

- **Peripheral blood counts:**
  No circulating blasts
  Neutrophil count ≥1.0 $x10^9$/L
  Platelet count ≥100 $x10^9$/L

- **Bone marrow aspirate and biopsy:**
  ≤5% blasts
  No Auer rods
  No extramedullary leukemia

Complete Remission with Incomplete Blood Count Recovery (CRi):

- **Peripheral blood counts:**
  No circulating blasts
  Neutrophil count <1.0 $x10^9$/L, or
  Platelet count <100 $x10^9$/L

- **Bone marrow aspirate and biopsy:**
  ≤ 5% blasts
  No Auer rods
  No extramedullary leukemia

Partial Remission (PR):

- All CR criteria if abnormal before treatment except:
  ≥50 % reduction in bone marrow blast but still >5% or
  Marrow blasts <5% with persistent Auer rods

Progressive Disease:

- death due to any cause
- start of non-protocol therapy directed for AML
- relapse as defined as
  - circulating blasts in peripheral blood
  - >5% blasts in marrow not attributable to any other cause

Progression Free Survival will be assessed in two ways: Time to disease progression or death, whichever occurs first, starting when crenolanib administration is begun and when stem cell infusion was performed (Day 0). BMA will be scheduled at the following time points: On day 100 ± 10, 6th month ± 1 month, 1st year ± 1 month and 2 years ± 2 months after allogeneic stem cell

transplantation. Patients may have repeat bone marrow evaluation any time when deemed necessary by the treating physician.

11. ADVERSE EVENT REPORTING

11.1 Adverse Event

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with study treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Adverse Events (AEs) will be evaluated according to the NCI CTCAE version 4.03 and documented in the case report form (CRF). After the Informed Consent Form is signed, study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease. During the study, site personnel will record any change in the pre-existing condition(s) and the occurrence and nature of any new adverse events. All adverse events of grade 3, grade 4, or grade 5, regardless of the relationship to the study drug, either expected or unexpected, must be recorded, graded, and reported to the Sponsor.

<u>Expected events post-transplant are:</u>

1) Febrile or infection episodes not requiring management in the intensive care unit
2) Preexisting side effects related to prior disease specific therapy including GVHD related symptoms (Sinusoidal Obstruction Syndrome (SOS), rash etc.) or ongoing medications for management of non-leukemia conditions (Diarrhea, mucositis etc.)
3) Myelosuppresion and myelosuppression-related events
4) Bone, joint, or muscle pain
5) Fatigue/malaise
6) Weakness
7) Alopecia

<u>General Therapy Related Events:</u>

1). Catheter related events (thrombosis, bleeding, infection)
2). Rash related to antibiotic use or GVHD
3). Hospitalization for the management of any of the above expected events

Reporting Hematology and Blood Chemistry Results:

- Data captured in addition to the protocol specified scheduled visit is to be reported on CRFs; this includes grade 3 and grade 4 laboratory abnormalities, independent of impact on dosing or associated signs and symptoms
- Transfusion information is to be captured throughout the study.

Adverse Event Reporting in 30-day Follow-up Period:

- Adverse events will be captured from the time the patient signs consent until 30 days after the last dose of study drug or until start of new study drug.
- If the patient with active AE goes on to another clinical study or standard therapy within the 30 day post-discontinuation follow up, active adverse events should continue to be captured until resolution for minimum of 30 days, if possible. Data should include name of new therapy.
- Patients who do not have progressive disease but stop crenolanib for toxicity should be followed until resolution of toxicity.
- Patients who have progressive disease and do not receive further therapy do not need to be followed, unless there is toxicity related to study drug which is unresolved at the time patient is taken off study

11.2 Serious Adverse Event Reporting

A serious adverse event (SAE) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A pregnancy or congenital anomaly/birth defect.
- Important medical events that do not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Any important medical event may be reported as an SAE if deemed appropriate by the Principal Investigator and the IND Sponsor.

All serious adverse events occurring during the conduct of a protocol will be reported (either via expedited report or log) to the IRB in accordance with the timeframes and procedures.

All serious adverse events will be recorded in the case report form.

Hospitalizations for the management of any expected adverse events (previously described) will not have an expedited report but it will be included in the annual report via the SAE log.

- All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to AROG.
- The institution's Internal SAE Report Form for Prompt Reporting will be used for reporting to AROG.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day post-discontinuation time period that is related to the study treatment must be reported to IRB and to AROG. This may include the development of a secondary malignancy.

11.3 Reporting of a Serious Adverse Event to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (AROG) according to 21 CFR 312.32.

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12. STATISTICAL CONSIDERATIONS

12.1 Preliminaries

This is a single-arm, Phase II study of crenolanib in allogeneic stem cell transplant in patients with acute myeloid leukemia (AML) in CR after allogeneic stem cell transplantation. Administration of crenolanib is oral, and will be started at some time between 42 and 90 days post-transplant, and then given every day for up to two years. There are two patient subgroups: 1) those that were in complete remission (CR) at the time of transplant, and 2) those that were not in complete remission (NCR) at the time of transplant. The primary outcome is progression-free survival (PFS) time, defined as the time to disease progression or death, whichever occurs first, starting when crenolanib administration is begun. A maximum of 24 patients will be enrolled in each subgroup.

12.2 Futility Monitoring

PFS time will be monitored separately within each of the two subgroups, using the Bayesian method of Thall et al. [1]. Denote standard therapy by S and the experimental crenolanib therapy by E. Assume that TS = PFS time with S follows an exponential distribution with median mS and

that TE = PFS time with E in the each subgroup follows an exponential distribution with median mE. Denote the median PFS times for the standard and experimental therapies by mS and mE, respectively. Under a Bayesian model, both mS and mE are assumed to follow Inverse Gamma(a, b) priors.

12.2.1 Futility Monitoring for the CR Subgroup

From historical experience, it will be assumed that Prob(TS > 12 months) = 0.67, which implies that the median PFS is 20.77 months. Assume that mS follows an Inverse Gamma (28.96, 580.77) prior, which has a mean of 20.77 and a variance of 16, and that mE follows an Inverse Gamma (3, 41.54) prior, which has the same mean of 20.77 months but a much higher variance of 431.5. The possibly right-censored times TE will be monitored continuously throughout the trial. Accrual into the CR subgroup will be terminated due to futility at any time if Prob (mS < mE | data) < 0.0785. The operating characteristics of this monitoring rule were developed using the program TTEDesigner version 1.2.2, available from the MDACC Department of Biostatistics, assuming an accrual rate of 1 patient per month. The operating characteristics (OCs) OCs for the CR subgroup rule are summarized in the Table 1.

Table 1. Operating characteristics of the design for the CR subgroup, assuming an accrual rate of 1 patient per month, with maximum sample size 24.

True Median PFS (months)	Pr (Stop Early)	Mean Sample Size
12	0.62	17.4
16	0.31	20.8
20.77	0.12	22.5
28	0.05	23.4
36	0.02	23.8

12.2.2 Futility Monitoring for the no CR Subgroup

For the NCR subgroup, under the Bayesian model, mS and mE follow Inverse Gamma(a, b) priors. From historical experience, it is assumed that Prob(TS > 12 months) = 0.21, which implies that the median is 5.33 months. Assume that mS follows an Inverse Gamma (14.63, 72.63) prior, which has a mean of 5.33 and a variance of 2.25, and that mE follows an Inverse Gamma (3, 10.66) prior, which has the same mean of 5.33 months but a much higher variance of 28.4 months. Possibly right-censored TE will be monitored continuously throughout the trial. Accrual into the NCR subgroup will be terminated is at any time if Prob(mS < mE | data) < 0.0795. The OCs of this monitoring rule were developed using the program TTEDesigner v. 1.2.2, available from the MDACC Department of Biostatistics, assuming an accrual rate of 1 patient per month. These OCs for the NCR subgroup rule are summarized in Table 2.

Table 2. Operating characteristics of the design for the NCR subgroup, assuming an accrual rate of 1 patient per month, with maximum sample size 24.

True Median PFS (months)	Pr (Stop Early)	Mean Sample Size
2	0.99	8.3
4	0.32	19.9
5.33	0.10	22.5
8	0.02	23.8
10	0.005	23.9

Both monitoring rules will be applied by use of the MDACC Department of Biostatistics Clinical Trial Conduct website, https://biostatistics.mdanderson.org/ClinicalTrialConduct/. The study biostatisticians, Peter Thall and Roland Bassett should be consulted as necessary.

12.3 Secondary outcomes and data analyses

Secondary outcomes will include disease-free survival (DFS) time, overall survival (OS) time, graft-versus-host disease, and 100-day transplant-related mortality. Within each subgroup, CR and no CR, these events will be tabulated and the distributions of DFS and OS time estimated using the method of Kaplan and Meier [2].

12.4 Subject Disposition

A summary of patient disposition will be provided for each cohort and will include the following:

- Number of patients enrolled
- Number of patients who participate in each study phase (induction, consolidation, maintenance)
- Reasons for discontinuation from study treatment and follow-up
- Summary of major protocol violations

12.5 Subject Characteristics

Patient characteristics will be reported for each cohort, and will include a summary of the following:

- Demographics
- Baseline disease characteristics
- Pre-existing conditions

Other characteristics will be summarized as deemed appropriate.

12.6 Concomitant Therapy

Concomitant medication will be reported overall as well as summarized in a frequency table using the terms recorded on the CRF. If warranted, an attempt may be made to determine how concomitant medications are related to observed study outcomes.

12.7 Response Outcome and Methodology

Response criteria will be adapted from the International Working Group for AML, as stated in section 10.1.

12.8 Safety Analyses

All subjects will be evaluable for safety. Adverse events that occur after a subject is entered (signs informed consent), but before the patient receives study drug, will not be recorded on the CRF unless the investigator believes that the events may have been caused by a protocol procedure. Safety analyses will include summaries of the incidence of adverse events by maximum CTCAE grade (version 4.03; NCI 2010) that occur during the study treatment period or within 30 days of the last dose of study treatment or until alternate therapy is started, regardless of causality or relatedness to study drug. The safety-related outcomes that will be summarized include:

- Adverse events,
- TEAEs,
- SAEs,
- Deaths,
- Discontinuations due to adverse events,
- Extent of exposure to study drug treatment,
- Hospitalizations,
- Use of key concomitant medications.

Analyses for data with discrete dates (for example, death date and start/stop dates of concomitant medications) will be performed through 30 days after the patient has been discontinued from study treatment or until alternate therapy is started. Adverse events will also be analyzed in this time frame. After 30-day post-discontinuation follow-up, only those SAEs that are thought to be related to study treatment or protocol procedure should be reported immediately to AROG or its designee. For these events, the patient must be followed until the event has resolved or stabilized.

12.9 Criteria for End of Study

This study will be considered complete following the data cut-off date for the final analysis. Documentation of the data cut-off will be included in the master study file.

After the final analysis, if subjects are continuing to benefit from study treatment, they may be allowed to continue receiving study treatment for up to additional one year as part of planned maintenance.

Patient is considered “off therapy” when study drug stops for any reason and crenolanib therapy is not continued.

Patient is considered “off study” after completion of the 30 day safety follow up or upon death or upon start of a new therapy, whichever comes first.

13. DATA QUALITY MANAGEMENT

13.1. Data Safety Monitoring Plan

Adverse events will be monitored during the treatment and post-treatment follow-up periods. Adverse events will be monitored on a continuous basis by the Sponsor. The Sponsor will conduct a biweekly teleconference with the study site to review safety data from this trial. A more frequent evaluation will be performed if accrual is rapid. The Sponsor and its medical consultants will

convene to analyze the safety data at least every 3 months or when more than 20% (more than 1 patient of the first 5 patients enrolled, more than 2 patients of the first 10 patients enrolled, or more than 3 patients of the first 15 patients enrolled) of the subjects require crenolanib dose reduction during the first 2 cycles of therapy. The study will be halted, and these data will be presented to the Sponsor's safety monitoring team to decide whether the crenolanib dose should be modified for all future patients. Enrollment will be halted if an apparent increase is observed in the occurrence of one or more of the following outcomes:

- Early mortality due to any cause
- Expected, non-hematologic, crenolanib-related toxicity (CTCAE Grade 4)
- Unexpected, non-hematologic, crenolanib-related toxicity (CTCAE Grade 4)

14. PROTOCOL ADMINISTRATION

Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the sponsor and the IRB of the study center.

Archival of data

All patient data (including source data) generated in connection with this study will be kept in the archives of each respective institution per policy or for at least 2 years after the approval of crenolanib. All data will be available for inspection by company representatives of the Medical Department and by regulatory authorities.

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10. Randhawa, J.K., et al., *Results of a Phase II Study of Crenolanib in Relapsed/Refractory Acute Myeloid Leukemia Patients (Pts) with Activating FLT3 Mutations*. 2014: ASH Annual Meeting Abstracts.

Appendix I. Administrative Procedures

Protocol Amendments, Other Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to all the monitors and supporters of the protocol. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, the sponsor should be notified and the IRB/IEC/REB at the center should be informed within 10 working days or per institutional policy.
Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials (e.g. AROG Pharmaceuticals staff versus a CRO)
2. minor changes in the packaging or labeling of study drug.

Publication of Results

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and appropriate AROG Pharmaceuticals personnel. Authorship will be determined by mutual agreement. For multicenter studies it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and AROG Pharmaceuticals.

AROG Pharmaceuticals must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). AROG Pharmaceuticals will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential

information is not being inadvertently divulged and provide any relevant supplementary information.

Disclosure and Confidentiality

The investigator agrees to keep all information provided by AROG Pharmaceuticals in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by AROG Pharmaceuticals (protocols, investigators' brochures, case report forms and other material) will be stored appropriately to ensure their confidentiality. The information provided by AROG Pharmaceuticals to the investigator may not be disclosed to others without direct written authorization from AROG Pharmaceuticals as applicable, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

Discontinuation of Study

AROG Pharmaceuticals reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in AROG Pharmaceuticals standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
   Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).
4. The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to AROG Pharmaceuticals before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval. AROG Pharmaceuticals supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by AROG Pharmaceuticals before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the AROG Pharmaceuticals monitor after IRB/IEC/REB approval.

Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html

Appendix II. Inclusion/Exclusion Criteria Checklist

All subjects enrolled must meet eligibility criteria based on the Inclusion/Exclusion criteria detailed in the application and approved by the IRB. Alternatively the study site/institution internal form can be used.

I. Study Information

Protocol Title:	Phase II Study of Crenolanib Besylate Maintenance following Allogeneic Stem Cell Transplantation in Patients with FLT3-positive Acute Myelogenous Leukemia
Protocol Number:	ARO-009

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria (all must be YES) (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. History of AML according to World Health Organization (WHO) classification	☐	☐		
2. First allogeneic hematopoietic stem cell transplantation (HSCT) using myeloablative conditioning (MAC), non-myeloablative (NMA), or reduced-intensity conditioning (RIC) preparative regimens.	☐	☐		
3. FLT3-ITD or FLT3-D835 positive disease at any time during disease course.	☐	☐		
4. Hematopoietic stem cell source is either with peripheral blood, bone marrow or cord blood.	☐	☐		
5. Donor source is matched related, unrelated, haploidentical donor or cord blood.	☐	☐		

6. At the time of allogeneic HSCT: a. No more than 1 antigen mismatch at HLA-A, -B, -C, -DRB1 or -DQB1 locus for unrelated donor with peripheral blood and bone marrow as the hematopoietic stem cell source; and b. Bone marrow blast ≤ 10%	☐	☐		
7. No sooner than 42 days but no later than 90 days after allogeneic HSCT.	☐	☐		
8. Post-transplant bone marrow blast count ≤ 5% confirmed within 21 days (+4 days) prior to starting study therapy	☐	☐		
9. Evidence of donor engraftment as defined by institutional standard T cell chimerism > 50%.	☐	☐		
10. Adequate engraftment within 7 days prior to starting study therapy: ANC ≥ 1.0 x 10^9/L without daily use of myeloid growth factor; and platelet ≥ 25 x 10^9/L without platelet transfusion within 1 week	☐	☐		
11. Non-hematological toxicities ≤ Grade 2	☐	☐		
12. Serum creatinine ≤ 1.5 × ULN OR creatinine clearance ≥ 50mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal	☐	☐		
13. Adequate liver function within 24 hours of start of crenolanib administration: a. with serum AST ≤ 2 x ULN and ALT ≤ 2 x ULN b. and bilirubin within the normal range	☐	☐		
14. Acute graft-versus-host disease (GVHD) ≤ Grade 1, either no signs of chronic GVHD or mild chronic GVHD graded as limited disease	☐	☐		
15. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2	☐	☐		
16. Age ≥ 18 years with the capacity to give written informed consent	☐	☐		

17. Non-pregnant and non-nursing women of childbearing potential must have a negative serum or urine pregnancy test ("Women of childbearing potential" is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months)	☐	☐	☐	
18. Women of childbearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation and for 90 days following completion of therapy	☐	☐	☐	
Exclusion Criteria (all must be NO) (From IRB approved protocol)	**Yes**	**No**		**Supporting Documentation***
1. Bone marrow blast > 5% within 21 days (+ 4 days) of start of study drug	☐	☐		
2. Active GVHD grade ≥ 2	☐	☐		
3. Concurrent use of corticosteroids equivalent of prednisone at a dose > 0.5 mg/kg	☐	☐		
4. Active and/or untreated central nervous system (CNS) leukemia	☐	☐		
5. Concomitant therapies for treatment or control of leukemia.	☐	☐		
6. Use of any of the following after transplantation and prior to starting study therapy: a. Chemotherapeutic agents for therapy of AML (note that prophylactic use of these agents is allowed in this study, e.g., methotrexate for GVHD) b. Investigational agents/therapies c. Azacitidine, decitabine or other demethylating agents d. Lenalidomide, thalidomide and pomalidomide	☐	☐		

7. Uncontrolled infection	☐	☐		
8. Known positive for human immunodeficiency virus (HIV); active hepatitis B (HBV) or hepatitis C (HCV) infection	☐	☐		
9. Significant cardiac disease (New York Heart Association classes III or IV) or unstable angina despite medication	☐	☐		
10. Pregnant or breast-feeding	☐	☐	☐	
11. Major surgery within 4 weeks of starting drug	☐	☐		
12. Receipt of investigational agents within 5 half-lives of last dose of investigational agent	☐	☐		
13. Prior treatment with crenolanib with progression on treatment	☐	☐		

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

This subject is **[**☐ **eligible** / ☐ **ineligible**] for participation in the study.

Signature:	Date:
Printed Name:	

Appendix III. Patient Diaries: Crenolanib

Cycle No: _____

This section to be completed by Site Study Staff ONLY

SUBJECT ID | | | | | | | | |

SUBJECT INITIALS | | | |

Investigational Drug: Crenolanib besylate (CP-868,596-26)

Protocol ID: ARO-009

Prescribed Dose: _____ mg TID, Dosing: _____ 100 mg tablets _____ 20mg tablets

Patient Diary: Week 1, Crenolanib besylate (CP-868,596-26) Investigation

PLEASE COMPLETE THIS DIARY CARD EACH DAY FOR THE SEVEN DAYS AFTER ADMINISTRATION OF INVESTIGATIONAL DRUG.
PLEASE READ ALL DIRECTIONS AND DEFINITIONS CAREFULLY BEFORE COMPLETING THE DIARY CARD.
PLEASE RETURN THIS DIARY CARD AT YOUR NEXT VISIT.

Day	Date (m m / d d / y y)	Time Taken (HR:MIN AM/PM)	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If dose skipped, please provide the reason/s.	With food?	If yes, please provide description of meal.	Any side effects (Please complete adverse events form in detail)
1		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
2		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
3		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
4		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
5		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
6		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
7		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		

Cycle No: _____

This section to be completed by Site Study Staff ONLY

SUBJECT ID | | | | | | | | | SUBJECT INITIALS | | | |

Investigational Drug: Crenolanib besylate (CP-868,596-26)

Protocol ID: ARO-009

Prescribed Dose: _____ mg TID, Dosing: _____ 100 mg tablets _____ 20mg tablets

Patient Diary: Week 2, Crenolanib besylate (CP-868,596-26) Investigation

PLEASE COMPLETE THIS DIARY CARD EACH DAY FOR THE SEVEN DAYS AFTER ADMINISTRATION OF INVESTIGATIONAL DRUG.
PLEASE READ ALL DIRECTIONS AND DEFINITIONS CAREFULLY BEFORE COMPLETING THE DIARY CARD.
PLEASE RETURN THIS DIARY CARD AT YOUR NEXT VISIT.

Day	Date (m m / d d / y y)	Time Taken (HR:MIN AM/PM)	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If dose skipped, please provide the reason/s.	With food?	If yes, please provide description of meal.	Any side effects (Please complete adverse events form in detail)
8		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
9		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
10		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
11		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
12		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
13		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
14		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		

Cycle No: _____

This section to be completed by Site Study Staff ONLY

SUBJECT ID | | | | | | | | |

SUBJECT INITIALS | | | |

Investigational Drug: Crenolanib besylate (CP-868,596-26)

Protocol ID: ARO-009

Prescribed Dose: _____ mg TID, Dosing: _____ 100 mg tablets _____ 20mg tablets

Patient Diary: Week 3, Crenolanib besylate (CP-868,596-26) Investigation

PLEASE COMPLETE THIS DIARY CARD EACH DAY FOR THE SEVEN DAYS AFTER ADMINISTRATION OF INVESTIGATIONAL DRUG.
PLEASE READ ALL DIRECTIONS AND DEFINITIONS CAREFULLY BEFORE COMPLETING THE DIARY CARD.
PLEASE RETURN THIS DIARY CARD AT YOUR NEXT VISIT.

Day	Date (m m / d d / y y)	Time Taken (HR:MIN AM/PM)	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If dose skipped, please provide the reason/s.	With food?	If yes, please provide description of meal.	Any side effects (Please complete adverse events form in detail)
15		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
16		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
17		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
18		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
19		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
20		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
21		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		

Cycle No: _____

This section to be completed by Site Study Staff ONLY

SUBJECT ID | | | | | | | | |

SUBJECT INITIALS | | | |

Investigational Drug: Crenolanib

Protocol ID: ARO-009

Prescribed Dose: _____ mg TID, Dosing: _____ 100 mg tablets _____ 20mg tablets

Patient Diary: Week 4, Crenolanib besylate (CP-868,596-26) Investigation

PLEASE COMPLETE THIS DIARY CARD EACH DAY FOR THE SEVEN DAYS AFTER ADMINISTRATION OF INVESTIGATIONAL DRUG.
PLEASE READ ALL DIRECTIONS AND DEFINITIONS CAREFULLY BEFORE COMPLETING THE DIARY CARD.
PLEASE RETURN THIS DIARY CARD AT YOUR NEXT VISIT.

Day	Date __ __/__ __/__ __ (m m d d y y)	Time Taken (HR:MIN AM/PM)	Number of Tablets Taken (100 mg Tablet)	Number of Tablets Taken (20 mg Tablet)	If dose skipped, please provide the reason/s.	With food?	If yes, please provide description of meal.	Any side effects (Please complete adverse events form in detail)
22		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
23		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
24		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
25		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
26		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
27		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
28		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		
		___:___ AM/PM				☐ Yes ☐ No		

Appendix IV. Study Calendar

Cycle No.	Screening	C1		C2	CN	Follow up
Relative day within each cycle	(-) D-7	D1	D14	DN	DN	
Informed Consent	X					
Inclusion/Exclusion	X					
Relevant Medical history, Demographics and Physical Exam	X					
FLT3 mutations[a]	X					
HIV, HepB, HepC[a]	X					
Serum or urine Pregnancy test	X	X			X	
Height	X					
Concomitant medications	X	X	X	X	X	
Vitals, ECOG, Weight	X	X		X	X	
Hematology[b]	X	X	X	X	X	
Blood Chemistry[b]	X	X	X	X	X	
Peripheral blood for PK analysis[c]		X		X	X*	
Peripheral blood for correlative analysis[d]		X				
Bone marrow aspirations[e]	X				X	
Adverse Event	X	X	X	X	X	X

[a] Unless previously drawn or tested prior to HSCT

[b] CBC and chemistry panel must be obtained within 24 hours prior to the first dose of crenolanib and on D1 (+ 2 days) and D14 (±7 days) during the first 14 days of maintenance then q28days (± 7 days). CBC and chemistry panels per local non-1572 physician is allowed to be used for this assessment but must be reviewed by the study investigator within the protocol specified timeframe. Results are to be recorded in the CRF. CBC and chemistry panel at the study site to be done no less than every 3 cycles.

[c, d] Peripheral blood for correlative analysis including Pharmacokinetics Assay will be obtained at multiple time points: C1D1 at 120 (± 15) minutes, 4 (±1) hours, and 8 (±2) hours after crenolanib administration, C2D1 at pre dose and at 3 (± 1) hours after crenolanib administration and finally on *C**3**D1 at pre dose and 3 (± 1) hours after crenolanib administration.
Further collections may be as requested by sponsor. Additional samples may be drawn at the discretion of the investigator.

[e]Baseline bone marrow aspirations should be collected within 21 days (+ 4 days) prior to start of crenolanib therapy. Bone marrow aspiration will be done as per institutional protocol during maintenance as long as criteria for CR are maintained. At loss of CR, if bone-marrow sample is obtained for clinical purposes to exclude toxicity issues (such as persistent pancytopenia due to study drug vs from progressive AML.), a sample is requested to also be sent to Propath (see Appendix XIII). Aspiration samples for

study purposes may also be submitted for subjects not in CR if a marrow will be done for clinical purposes.

Appendix V. Definition of a Serious Adverse Event (SAE)

Life threatening: "Life threatening" means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life threatening" does not mean that had an adverse event occurred in a more severe form it might have caused death (i.e., hepatitis that resolved without hepatic failure).

Hospitalization: Outpatient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled on the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention: Medical and scientific judgment should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Disease progression: Any events or hospitalizations that are unequivocally due to progression of disease must not be reported as serious adverse events.

The following factors should be considered when deciding if there is a "reasonable possibility" that an adverse event may have been caused by the investigational product.

- Time course of events and exposure to suspect drug: Has the patient actually received the suspect drug? Did the adverse event occur in a reasonable temporal relationship to the administration of suspect drug?
- Consistency with known drug profile: Was the adverse event consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same

pharmacological class? OR could the adverse event be anticipated from its pharmacological properties?

- De-challenge experience: Did the adverse event resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause: The adverse event cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience: Did the adverse event reoccur if the suspected drug was reintroduced after having been stopped? Laboratory tests: Has a specific laboratory investigation confirmed the relationship?

A “reasonable possibility” could be considered to exist for an adverse event when 1 or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply, or if there is evidence of exposure and a reasonable time course, but any de-challenge (if performed) is negative or ambiguous, or there is another more likely cause of the adverse event.

In difficult cases, other factors could be considered such as the following:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as having a “reasonable possibility” of causal relationship, unless additional evidence becomes available to refute this.

If true progression is determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

Appendix VI. Laboratory manual

Pharmacokinetic Assay

ONLY FOR SELECTED SITES. The participating institution will request a Pharmacokinetics (PK) Kit from AROG Pharmaceuticals to perform PK on each patient enrolled on the study. Site should contact Arog Pharmaceuticals at info@arogpharma.com or 1 214.593.0515 to request a Pharmacokinetics Kit.

Sampling Strategy: USE THE PK KIT PROVIDED BY THE SPONSOR
Peripheral blood for pharmacokinetic studies will be drawn at the following points:

Day 1 of Cycle 1 (first day of crenolanib treatment)

a. post-dose 120 minutes (± 15 minutes)
b. post-dose 4 hours (± 30 minutes)
c. post-dose 8 hours (± 2 h)

Day 1 of Cycle 2

a. pre-dose
b. post-dose 3 hours (± 60 minutes)

Day 1 of Cycle 3

a. pre-dose
b. post-dose 3 hours (± 60 minutes)

Sampling Collection and Processing Instructions

- At the sampling time point, collect 10 mL of whole blood for each time point in an appropriately labeled red/orange-top tube containing thrombin and completely cover with aluminum foil to protect from light.
- The whole blood will remain at room temperature until clotted (approximately 5 minutes).
- The serum will be separated from whole blood by centrifugation at 1500xG for 10 minutes. Minimize light exposure during this process.
- Prepare screw-capped polypropylene collection tubes labeled with UPIN, date and time of collection.
- The serum will be transferred to the appropriate tubes and covered with aluminum foil if not immediately frozen. Store at -80^{o}C within 1 hour of collection.
- Samples from each individual patient will be stored and batched for that patient. The date and time of sample collection, crenolanib dose, and **date and time of the last crenolanib dose** should be recorded on the appropriate Pharmacokinetics Data Collection Form (Forms 1, 2, 3 and 4).

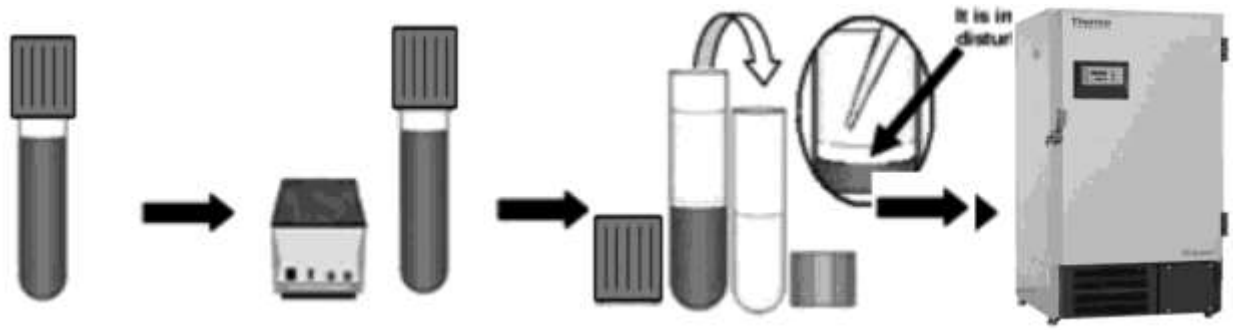
Sampling Handling and Shipping Instructions

- Samples should be shipped within **30 days** of the last sample collection, whenever feasible. Specimens collected should be shipped via **FedEx Priority Overnight** shipping for delivery Tuesday through Thursday. Weekend and holiday deliveries should be avoided.
- In preparation of shipping samples, contact AROG Pharmaceuticals at info@arogpharma.com and Cynthia Gomez at CGomez@microconstants.com to notify of sample shipment and to provide the FedEx tracking number. AROG will provide a confirmation regarding receipt of email concerning the shipment to the site.
- Ship all pharmacokinetic samples on dry ice, along with a completed Pharmacokinetics Data Collection Form to:

Cynthia Gomez
Senior Project Coordinator
MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121
P 858.652.4600 . F 858.652.4699
E CGomez@microconstants.com
www.microconstants.com

Additional Information

If any additional information is needed for pharmacokinetic sampling, storage or shipment, please contact AROG Pharmaceuticals.
AROG Pharmaceuticals, LLC
E: info@arogpharma.com
O: +1 214.593.0500
F: +1 214.594.0002



PROTECT SPECIMEN FROM LIGHT. Allow the whole blood to remain at room temperature for approximately 30 minutes to clot

Centrifuge the clotted blood at 1500xG for 10 minutes

Transfer the serum layer to the appropriately labeled tubes. PROTECT FROM LIGHT IF NOT IMMEDIATELY STORING IN FREEZER.

Store the serum samples at -80°C within 1 hour of collection

Figure 1: Sampling collection and processing instructions for Pharmacokinetic Assay

FORM 1 ARO-009 C1D1Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Total daily Crenolanib Dose (mg):	Today's Date:	

Fill in crenolanib dose date, time, and tolerance in the spaces below. List the scheduled and actual times of the pharmacokinetic samples in the chart below. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Date of Dose:

_____

Dose Administration Time:

_____

Describe Dose Tolerance:

_____

Course 1 Day 1	Date	Scheduled Time	Actual Time
post crenolanib 120 minutes (±15 minutes)			
post crenolanib 4 hours (±30 minutes)			
post crenolanib 8 hours (±2 h)			

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

FORM 2 ARO-009 C_D_ Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Total daily Crenolanib Dose (mg):	Today's Date:	
Please mark cycle above		

Fill in crenolanib dose date, time, and tolerance in the spaces below. **Do not take second dose of crenolanib until 3h PK time point has been drawn.** List the scheduled and actual times of

the pharmacokinetic samples in the chart below. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Date of Dose:

_____

Dose Administration Time:

_____

Describe Dose Tolerance:

_____

C_D_	Date	Scheduled Time	Actual Time
Prior to crenolanib dose (pre)			
post crenolanib 3 hours (±60 minutes)			

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

Bone Marrow Aspiration and Whole Blood Collection

Sampling Schedule for Bone Marrow Aspirates

Bone marrow aspirates for research purposes will be collected at the time of routine marrow sampling with 1 additional aspiration of about 5 ml drawn for study purposes and placed in heparinized cell preparation tubes. The following are suggested time points, and after the first induction, bone marrow should be performed at the discretion of the treating physician.

- Screening
- Maintenance: as per the institutional standard of care
- When patient is determined to have progressive disease by the treating physician (loss of CR/CRi).

Sampling Schedule for whole blood

One sample of 10 mL of whole blood for each time point is drawn and placed in heparinized cell preparation tubes for other correlative science research studies. See FORMS 5 or 6. Sample should be drawn at the following two time points:

- Pre administration of first dose of crenolanib.
- When patient is determined to have progressive disease by the treating physician.

Sampling collection and processing

- BMA/Blood will be done as per institutional bone marrow aspiration protocol. Sampling will consist of up to 5 mL of aspirated BMA sample or 10 ml of whole blood placed in heparinized cell preparation tubes.
- After collection of bone marrow or whole blood, store tube upright at room temperature until centrifugation. BMA/Blood samples should be centrifuged within one hours of blood collection for best results.
- NOTE: Remix the BMA/blood sample immediately prior to centrifugation by gently inverting the tube 8 to 10 times. Also, check to see that the tube is in the proper centrifuge carrier/adapter.
- Centrifuge marrow/blood sample at room temperature (18-25ºC) in a horizontal rotor (swing-out head) for a minimum of 20 minutes at 1500 to 1800 RCF (Relative Centrifugal Force).
- After centrifugation, mononuclear cells and platelets will be in a whitish layer just under the plasma layer (see Figure 2 below). Aspirate approximately half of the plasma without disturbing the cell layer.
- Collect cell layer with a Pasteur pipette (provided by AROG) and transfer to 3 cryopreservation tubes (provided by AROG) and centrifuge at 3000 rpm for 5 min. Remove all liquid and either snap freeze cell pellet in liquid nitrogen or dry ice and then store -80ºC immediately.
- Samples from each individual patient will be stored and batched for that patient. Please complete appropriate Data Collection Form (FORMS 5 or 6).

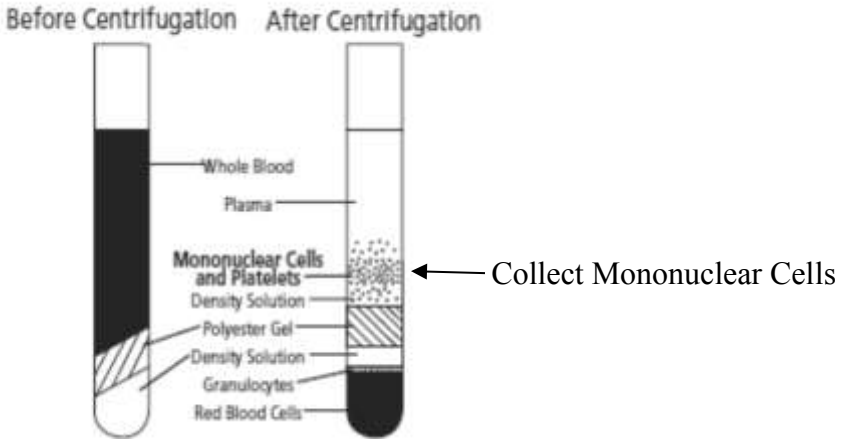


Figure 2 Layering of formed elements in the cell preparation tubes

Shipping of Samples

- In preparation of sample shipping, contact AROG Pharmaceuticals at svali@arogpharma.comand site at debra.cohen@propath.com to notify of sample shipment and to provide the FedEx tracking number. AROG Pharmaceuticals will provide a confirmation regarding receipt of email concerning shipment to the site.
- Samples can be shipped at intermediate times along with Data Collection Form to:

Debra Cohen
Cytogenetics and Molecular Laboratory Manager
ProPath
1355 River Bend Drive
Dallas TX 75247
214.237.1739
debra.cohen@propath.com
www.ProPath.com

Contact Information for notification of bone marrow aspiration samples:

AROG Pharmaceuticals, LLC
E: svali@arogpharma.com
O: +1 214.593.0519 (Sheetal Vali)
F: +1 214.594.0002

FORM 3 ARO-009 Whole Blood Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	**Weight (kg):**	
Crenolanib Dose (mg) and time of ingestion:		**Today's Date:**
Please indicate phase of therapy:	Screening	Follow up

List the name, dose, and regimen of other drugs the patient has received within 48 hours of crenolanib therapy, including any vitamins and herbal supplements (St. John's Wort, etc.).If more space is needed, please use an additional sheet:

Drug Name	Drug Dose	Date and Time Administered

List the type, quantity, and time of food/drink consumed 1 hour prior to crenolanib dose until 2 hours post crenolanib dose. Use an additional sheet if necessary.

_____

_____

_____

Fill in <u>exact</u> dose dates, times, and tolerances for the <u>prior 4</u> crenolanib doses in the spaces below.

Crenolanib Date and Time Administered	Crenolanib Dose	Crenolanib Tolerance

List the scheduled and actual times of the collected samples in the chart below. List exact date and time of crenolanib administration. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible.

Samples	Date	Scheduled Time	Actual Time

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____
Date: _____

FORM 4 ARO-009 Bone Marrow Aspiration C_ D_ Data Collection Form

Study Acc #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
Total daily Crenolanib Dose(mg):	Crenolanib Dosage (mg/m^2):	Today's Date:
Please indicate phase of therapy: Induction	Consolidation	Maintenance

Please fill in crenolanib dose date, time, and tolerance in the spaces below. List sample volume or estimated mass, and note any collection issues in the chart below. Use an additional sheet if necessary.

Date of Dose:

_____

Dose Administration Time:

_____

Describe Dose Tolerance:

_____

Bone Marrow Aspiration	**Sample Volume or Estimated Mass**	**Note any collection issues**	**Date**
Sample – 1			
Sample – 2			

Name of person completing form: _____
Phone Number: _____
Email: _____
Date: _____

Appendix VII. Contact Information AROG Pharmaceuticals

Contact Information of Medical Monitor

James Strauss, M.D.
AROG Pharmaceuticals, Inc.
Email: jstrauss@arogpharma.com
Phone (O): (214) 593-0525
(M): (214) 536-6861
Fax: 214.594.0002

Contact Information of Director of Clinical Operations

Abhijit Ramachandran
AROG Pharmaceuticals, Inc.
Email: aramachandran@arogpharma.com
Office: 214.593.0515
Mobil: 817.849.0175
Fax: 214.594.0002

Contact Information of Study Monitors

Vinoo Urity
AROG Pharmaceuticals, Inc.
Email: vurity@arogpharma.com
Phone: 214.593.0521

Contact Information for notification of shipment of correlative studies samples

AROG Pharmaceuticals, Inc.
Email: info@arogpharma.com
Office: +1 214.593.0500
Fax: +1 214.594.0002

Appendix VIII. Shipping Addresses for Serum and Tissue Samples

A. Pharmacokinetics Samples
Cynthia Gomez
Senior Project Coordinator
MicroConstants, Inc.
9050 Camino Santa Fe
San Diego, CA 92121
P (858) 652-4600
F (858) 652-4699
CGomez@microconstants.com
www.microconstants.com

B. Bone Marrow Aspirate and Whole Blood samples
ProPath
1355 River Bend Drive
Dallas TX 75247
Attn: Debra Cohen, Cytogenetics and Molecular Laboratory Manager
214.237.1739
www.ProPath.com

Appendix IX. CYP3A4 drugs potentially affecting crenolanib pharmacokinetics

The following are few examples of therapeutic agents which are potential hepatic enzyme (CYP3A4) inducing or inhibiting drugs and **should be used with caution in** patient participation on the study):

Strong Inducers	**Strong Inhibitors**
phenytoin (anticonvulsants and mood stabilizers)	telithromycin (macrolide antibiotics)
carbamazepine (anticonvulsants and mood stabilizers)	clarithromycin (macrolide antibiotics)
oxcarbazepine (anticonvulsants and mood stabilizers)	ketoconazole (azole antifungals)
phenobarbital (barbiturates)	itraconozole (azole antifungals)
rifampin (bactericidal)	nefadozone (antidepressant)
modafinil (stimulant)	Saquinavir (HIV protease inhibitor)
dexamethasone	
hyperforin (constituent of St. John's Wort)	Suoxone (analgesic)
glucocorticoids	
Rifabutin (antimycobiotic)	
Troglitazone (anti-diabetic and anti-inflammatory drug)	

Moderate Inducers	**Moderate Inhibitors**
pioglitazone (Thiazolidinedione)	erythromycin (macrolide antibiotics)
	fluconazole (azole antifungals)
	aprepitant (antiemetic)
	bergamottin (constituent of grapefruit juice)
	verapamil (calcium channel blocker)
	Diltiazem (calcium channel blocker)