Protocol ARO-005

A Phase II Study of Crenolanib in Relapsed/Refractory Acute Myeloid Leukemia Patients with FLT3 Activating Mutations

Version 3.0

Confidential Information

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1. OBJECTIVES

1.1 Primary Objectives:

- To determine the response rate to crenolanib, including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR), in relapsed/refractory AML patients with FLT3 activating mutations after first cycle (28-days) and at best response.
- To determine the safety and tolerability of crenolanib in AML patients with FLT3 activating mutations

1.2 Secondary Objectives:

- To determine the duration of response in AML patients with activating FLT3 mutations treated with crenolanib
- To determine the progression free survival and overall survival of AML patients with activating FLT3 mutations treated with crenolanib
- To characterize crenolanib pharmacokinetics in adult patients with AML and relate crenolanib exposure to outcome (e.g., toxicity and/or FLT3 inhibition)
- To analyze phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples

2. SYNOPSIS

Study Rationale

Activating mutations of FLT3 including internal tandem duplication (ITD) mutations within the juxtamembrane domain and single base pair mutations within the tyrosine kinase domain (TKD) of the receptor are the most frequent mutations described in AML, with a prevalence of approximately 30%. Despite the presence of these mutations, there is no approved target specific therapy for AML patients who harbor them.

Crenolanib besylate (CP-868,596-26) is an orally bioavailable, selective tyrosine kinase inhibitor (TKI) of both wild-type FLT3 as well as FLT3 with activating mutations. Crenolanib has a high affinity for mutant FLT3 with K_d values of 0.43nM, 0.18nM, and 0.4nM for FLT3 ITDs and TKD mutations D835Y and D835H, respectively. This high affinity of crenolanib allows it to inhibit aberrant FLT3 signaling at clinically achievable concentrations in AML patients. The activity of crenolanib against wild type FLT3 and FLT3 with activating mutations has been confirmed in both myeloid leukemia cell lines as well as in primary leukemic blasts obtained from patients. Crenolanib was found to be cytotoxic to leukemic blasts from treatment naïve patients with FLT3 activation as well as patients whose leukemia had progressed after chemotherapy or treatment with other FLT3 TKIs.

This pilot Phase II study is designed to evaluate the efficacy and tolerability of crenolanib in two cohorts of AML patients with FLT3 activation mutations (patients whose leukemia has recurred after prior chemotherapy not including a FLT3 TKI and patients whose leukemia has progressed after prior therapy with a FLT3 TKI).

Clinical Protocol Synopsis

Protocol Number: ARO-005

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

Title of Study: A Phase II Study of Crenolanib in relapsed/refractory Acute Myeloid Leukemia patients with activating FLT3 mutations.

Number of Planned Patients:
70 patients

Length of Study: 1 year

Objectives:

Primary Objectives

- To determine the response rate to crenolanib, including the rates of complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR), in relapsed/refractory AML patients with FLT3 activating mutations after first cycle (28-days) and at best response.
- To determine the safety and tolerability of crenolanib in AML patients with FLT3 activating mutations

Secondary Objectives

- To determine the duration of response in AML patients treated with crenolanib
- To determine the progression free survival and overall survival in AML patients with FLT3 activating mutations treated with crenolanib
- To characterize the pharmacokinetics of crenolanib in adult patients and relate drug disposition to outcome or pharmacodynamic markers (i.e. toxicity and/or FLT3 inhibition)
- To analyze phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples

Study Design:
This is a Phase II open label study of crenolanib besylate given three times a day (preferably every eight hours) continuously until one of the criteria for study discontinuation is fulfilled.

The study will enroll 2 different cohorts of patients in parallel.

Cohort A: Will enroll relapsed/refractory AML patients with FLT3 activating mutations who progressed on one or more prior chemotherapy regimens excluding a FLT3 TKI

Cohort B: Will enroll relapsed/refractory AML patients with FLT3 activating mutations whose leukemia has progressed and have history of prior therapy with one or more FLT3 TKIs.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Inclusion Criteria:

- Confirmed primary AML relapsed or refractory after prior therapy, AML secondary to antecedent chemotherapy or radiation therapy, or AML due to prior myelodysplastic syndrome (MDS)/ myeloproliferative neoplasm (MPN) as defined by WHO criteria with presence of either FLT3 ITD and/or other FLT3 activating mutations
- Patients with secondary AML should have failed no more than two (2) prior regimens
- Patients with antecedent MDS/MPN, defined by WHO criteria, without any prior therapy for AML, regardless of the number of therapies for MDS/ MPN
- Patients with primary AML should have received no more than two (2) prior cytotoxic containing salvage regimens. Reinduction with the same regimen or stem cell transplant will not be considered a separate salvage regimen. Change of drugs will be considered a salvage regimen. Unlimited FLT3 TKI therapy (even in combination with cytotoxics/hypomethylating agents) is allowed for patients enrolled in cohort B.
- Patients must have tested positive for FLT3-ITD and /or other FLT3 activating mutations within 30 day screening period.
- Males and females age ≥18 years
- ECOG PS 0-2
- Adequate liver function, defined as bilirubin ≤1.5x ULN, ALT ≤3.0x ULN, and AST ≤3.0x ULN.
- Adequate renal function, defined as serum creatinine ≤1.5x ULN
- Recovery from non-hematological toxicities of prior therapy (including HSCT) to no more than grade 1 (except alopecia)
- Subjects should have received no anti-leukemic therapy (except hydroxyurea) prior to the first dose of crenolanib as follows: for 14 days for classical cytotoxic agents and for five times the $t_{1/2}$ (half-life) for FLT3 inhibitors and antineoplastic agents that are neither cytotoxic nor FLT3 inhibitors (e.g. hypomethylating agent or MEK inhibitor). Refer to Appendix XVI for half-life information and drugs considered as FLT3 inhibitors for purposes of this trial.
- Negative pregnancy test for WOCBP.
- Able and willing to provide written informed consent.

Exclusion Criteria:

- Absence of a FLT3 activating mutation
- <5% blasts in blood or marrow at screening
- Concurrent chemotherapy, or targeted anti-cancer agents, other than hydroxyurea.
- Patient with concurrent severe and/or uncontrolled medical conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.
- HIV infection or active hepatitis B (defined as hepatitis B surface antigen positive) or C (defined as hepatitis C antibody positive)
- Known clinically active central nervous system (CNS) leukemia
- Patients less than 30 days post HSCT.
- Subjects who have clinically significant graft versus host disease requiring treatment and /or have >grade 2 persistent non hematological toxicity related to transplant
- Prior crenolanib treatment for a non-leukemic indication
- Major surgical procedures within 14 days of Day 1 administration of crenolanib.
- Unwillingness or inability to comply with protocol.

Test Product, Dosage and Mode of Administration: Crenolanib besylate, 100 mg TID (preferably every eight hours), taken orally at least 30 minutes pre or post meal. Patients will complete a daily diary to record the date, time and amount (number of tablets) of crenolanib taken and eating schedule. Concurrent hydroxyurea (maximum 5g total daily dose x 14 days) is permitted during the first 28 days of study therapy.
Planned Duration of Treatment: The anticipated duration of patient involvement is a minimum of 28 days with a maximum of 365 days but assessed individually for each patient. Patients will take crenolanib besylate daily until their disease has progressed, the patient has died, or the patient discontinues for adverse events, investigator's judgment, or other reasons Patients who have discontinued study drug will continue to be followed for 30-days post last dose.
Reference Therapy, Dose and Mode of Administration: No comparators will be used.
Criteria for Evaluation: International Working Group for AML (Cheson, et. al., JCO, 2003)
Statistical Methods: The primary end-point is overall response rate. The overall response rates in the two cohorts will be evaluated along with its 95% confidence interval at the end of cycle 1 (28-days) and at best response. Analysis of secondary endpoints will be predominantly descriptive statistics and will be interpreted as being exploratory and hypothesis generating. Duration of response, Progression Free Survival (PFS) and Overall Survival (OS) will be estimated using the method of Kaplan-Meier. In addition, if at any time unacceptable toxicity is encountered in greater than 30% of patients, accrual will be stopped and lower doses of crenolanib may be investigated.

3. BACKGROUND

Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is a malignancy of immature granulocytes or monocytes. Malignancy is characterized by accumulation of leukemic blasts and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. In hematologic malignancies, high levels of FLT3 expression have been detected in AML blasts (70%-100%).[1,2]

Targeted Therapy in AML

During the past 30 years there has been a steady improvement in the survival of patients diagnosed with AML. New drugs like arsenic trioxide and all-trans retinoic acid (ATRA) have been approved for acute promyelocytic leukemia and immunoconjugates like gemtuzumab ozogamicin were for a period approved for elderly AML patients. However, no new drugs have been approved for the treatment of FLT3 mutant AML.

Biological Role of FLT3

FMS-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase with important roles in hematopoietic stem/progenitor cell survival and proliferation. FLT3 belongs to the class III receptor tyrosine kinase (RTK) family, including FMS, c-KIT, platelet derived growth factor receptorα, and platelet-derived growth factor receptorβ. [2] The human FLT3 gene is located on chromosome 13q12 and encompasses 24 exons. It encodes a membrane-bound glycosylated protein of 993 amino acids with a molecular weight of 158-160 kDa, as well as a non-glycosylated isoform of 130-143 kDa that is not associated with the plasma membrane.[3,4] The schematic of FLT3 is provided in Figure 3.1.[5]

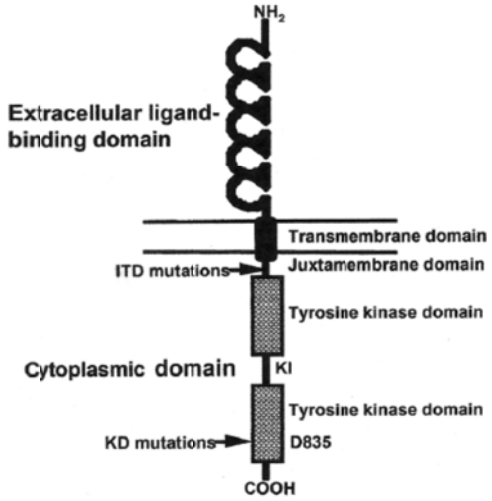


Figure 3.1. Schematic of FLT3 representing the domains: transmembrane, juxtamembrane and tyrosine kinase and the mutation locations of ITD and KD.[6]

In normal human hematopoiesis, FLT3 expression is restricted to immature hematopoietic progenitors including $CD34^+$ hematopoietic stem cells (HSCs). [7] FLT3-ligand (FL) stimulation

of hematopoietic progenitors without other growth factors prompts monocytic differentiation, whereas combinations of stem cell factor, interleukin (IL)-3, and FL induce proliferation and maintenance of human $CD34^+$/ $CD38^+$ progenitor cells.[8,9]

Downstream Pathways of Normal FLT3

Binding of the FLT3 ligand is followed by receptor autophosphorylation at tyrosine residues, thereby creating docking sites for signal transducing effector molecules and activating various signaling pathways. The downstream signaling cascade involves the tyrosine phosphorylation and activation of multiple cytoplasmic molecules. The FLT3 cytoplasmic domain physically associates with the p85 subunit of phosphoinositol-3-kinase (PI3K), Ras GTPase, phospholipase C-g, Shc, growth factor receptor bound protein (Grb2) and Src family tyrosine kinase, and results in the phosphorylation of these proteins.[11] These actions affect the activation of further downstream PI3K/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways.[12] Bruserud et al. reported that exogenous FL increases blast proliferation for not only patients with wild-type FLT3 but also patients with FLT3-ITD, as well as, FLT3-TKD mutations.[13] Therefore, FL-mediated triggering of FLT3 appears to be important for both wild-type and mutant FLT3 signaling.

FLT3 Mutations in AML

In hematologic malignancies, high levels of FLT3 expression have been detected in AML blasts (70%-100%).[14,15] Mutations within the FLT3 gene have been detected in up to 35% of acute myeloid leukemia (AML) patients and represents one of the most frequently identified genetic alterations in AML.[16] Two major classes of activating FLT3 mutations have been identified in AML patients: internal-tandem duplications (ITDs) and tyrosine kinase domain (TKD) point mutations (Figure 3.1).[5] ITDs in the juxtamembrane (JM) domain of FLT3 were first described by Nakao et al and are detected in 20%-25% of AML patients. ITDs are in-frame duplications of 3-400 base pairs. [17] Recently, FLT3-ITD insertion sites were systematically reviewed in 753 unselected patients with AML positive for FLT3-ITD, and it was demonstrated that 28.7% of ITDs integrate in the TKD1 and not as previously assumed in the JM domain of FLT3. [18] ITD mutations cause constitutive activation of FLT3, leading to aberrant activation of multiple downstream pathways such as phosphatidylinositol 3-kinase (PI3K)/AKT, mitogen-activated protein kinase/ extracellular signal-regulated kinase (MAPK/ERK), and signal transducer and activator of transcription 5 (STAT5). [18] FLT3-ITD expression confers factor independent growth in murine IL-3– dependent cell lines and causes a fatal myeloproliferative disorder in murine bone marrow (BM) transplantation models and in FLT3-ITD knock-in mice. [19]

A number of FLT3 inhibitors with *in vitro* and *in vivo* activity against the FLT3 ITD mutation are in clinical development. However, most AML patients who initially respond to these FLT3 TKIs experience relapse. This resistance is mediated through the development of the D835 FLT3 TKD secondary mutation in approximately 5-10% of relapsed AML patients. No FLT3 inhibitor currently in development has the ability to inhibit the FLT3 TKD mutation D835 to treat patients with relapsed AML

4. CRENOLANIB BESYLATE (CP-868,596-26), PRECLINICAL DATA

Crenolanib is a Potent Inhibitor of Type III Receptor Kinases

Crenolanib besylate (CP-868,596-26) is an orally bioavailable selective and potent inhibitor of FLT3, both wild type and FLT3 constitutively active mutations. The chemical name of crenolanib besylate is 4-piperidinamine, 1-[2-[5-[(3-Methyl-3-oxetanyl) methoxy]-1H-benzimidazol-1-yl]- 8-quinolinyl]-, monobenzenesulfonate. [26] The CAS registry number is 670220-93-6.[27]

Crenolanib is a specific and potent inhibitor of class III receptor tyrosine kinases (RTKs) (Table 4.1). Crenolanib has sub-nanomolar K_d against wild-type FLT3 (0.74nM) and is potent against PDGFRα (3.2 nM) and PDGFRβ (2.1nM) (Table 4.1.). Besides class III RTKs, crenolanib does not inhibit any other know RTK (VEGFR, FGFR) or any other serine/threonine kinase (Abl, Raf) at clinically achievable concentrations.

RTK	Crenolanib K_d
FLT3	**0.74 nM**
PDGFRβ	2.1 nM
PDGFRα	3.2 nM
CFS1R	30 nM
Kit	78 nM

Table 4.1. Activity of crenolanib against type-III receptor kinases[26]

Crenolanib has high affinity for constitutively active FLT3 mutants,

Crenolanib was evaluated in a K_dELECT assay (DiscoverRx, San Diego, CA) to determine its affinity against FLT3 and its mutant isoforms. The results demonstrate that crenolanib has activity against the FLT3-ITD, the most frequent FLT3 aberration in AML, and the FLT3-TKD D835H and D835Y mutations (Table 4.2).

KINOMEscan Gene Symbol	Publications that first report gene aberration in AML	Crenolanib K_d (nM)
FLT3		0.74
FLT3(ITD)	Leukemia. 10, 1911-1918 (1996).	0.43
FLT3(D835H)	Blood. 97, 2434-2439 (2001); Br J Haematol. 113, 983-988 (2001).	0.4
FLT3(D835Y)	Blood. 97, 2434-2439 (2001); Br J Haematol. 113, 983-988 (2001).	0.18
FLT3(K663Q)	Leukemia. 20, 2008-2014 (2006).	1.4
FLT3(R834Q)	Cancer Cell. 12, 501–513 (2007).	0.8

Table 4.2. K_d measurements for the interactions of crenolanib with wild type FLT3 and its mutants: FLT3-ITD, FLT3-TKD D835Y, and FLT3-TKD D835H.[26]

We compared the K_d of crenolanib for wild type and mutant FLT3 with the K_d's of 72 other TKIs.[19] Crenolanib binds to FLT3-ITD with a K_d of 0.43, as compared to a K_d of 8.8 nM for quizartinib and K_d of 13 nM for sorafenib. Crenolanib binds to FLT3-TKD D835H with a K_d of 0.4 nM, as compared to a K_d of 3.7nM for quizartinib and K_d of 30nM for sorafenib. Similarly, crenolanib also binds to FLT3-TKD D835Y, a mutation that has been shown to cause resistance to quizartinib, with a K_d of 0.18nM, as compared to a K_d of 7.1nM for quizartinib and K_d of 82nM for sorafenib (Figure 4.1).[19] In addition to the kinome scan, crenolanib inhibition of the FLT3 wild type and FLT3-TKD D835Y mutation was confirmed by Millipore IC50 profiler assay, a system that directly measures phosphorylation with superior sensitivity using phosphocellulose (PH) filter plates. Crenolanib showed potency at 2nM against the FLT3 D835Y mutation and 3 nm against wild type FLT3.

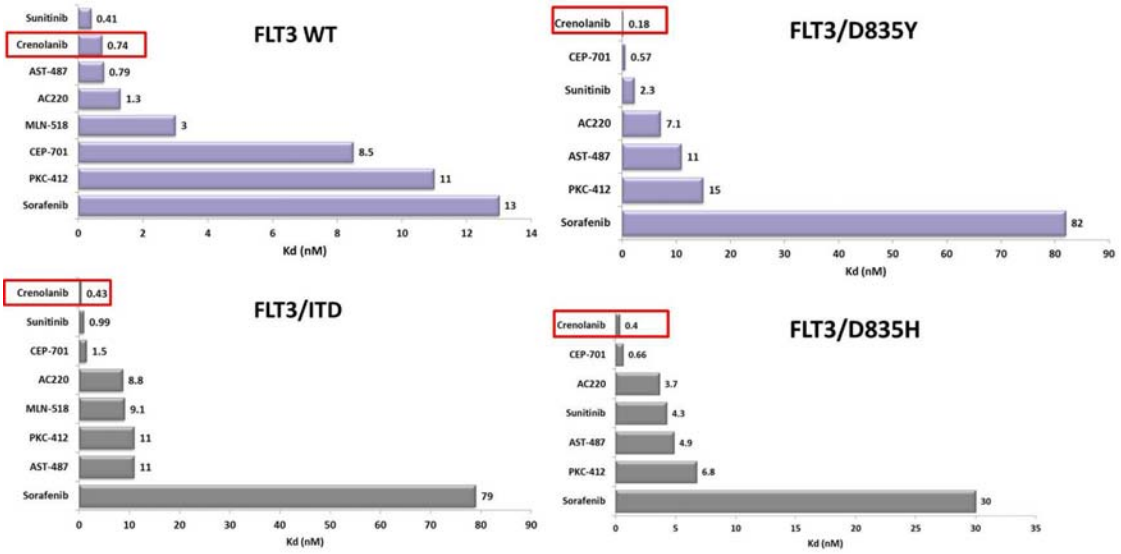


Figure 4.1. K_d measurements for the interactions of crenolanib, sunitinib, CEP-701, AC-220 (quizartinib), sorafenib etc, with wild type FLT3 and its mutants: FLT3-ITD, FLT3/D835Y, and FLT3/D835H. Assay signals were normalized to facilitate comparison.[28]

Immunoblot experiments confirm the activity of crenolanib against FLT3 and its mutants in different cells

In immunoblots, crenolanib inhibited phosphorylation of the wild type FLT3 receptor (in SEMK2 cells), the FLT3-ITD receptor (in Molm 14 and MV411 cells) and the FLT3-D835Y TKD mutation (in transfecting Ba/F3 cells), (Figure 4.2).

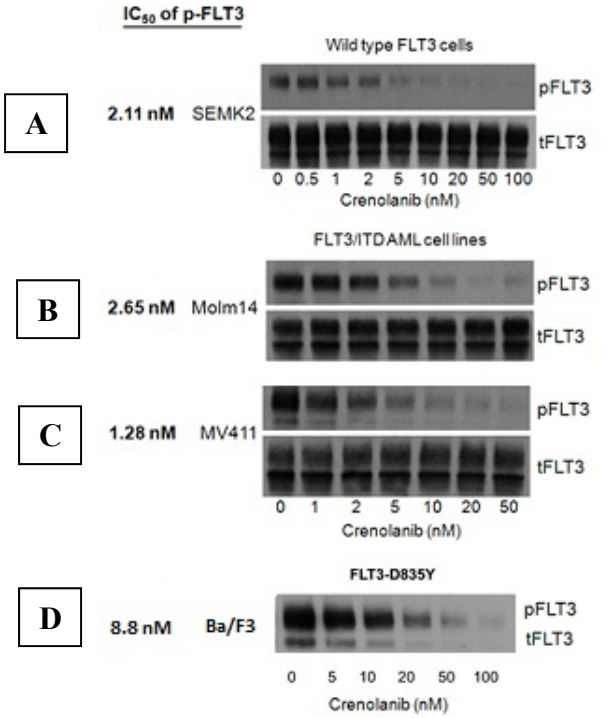


Figure 4.2 Dose response of crenolanib in various models of FLT3 AML cells: (A) SEMK2 cells, (B) Molm14 cells, (C) MV411 cells, and (D) FLT3-D835Y Ba/F3 cells.[27]

In SEMK2 cells that express wild type FLT3, crenolanib was effective with a p-FLT3 IC_{50} of 2.11nM.The IC_{50} values of crenolanib against the TF/ITD Molm14 and MV411 cell lines, derived by transfecting TF-1 cells, were 2.65nM and 1.28 nM, respectively. The IC_{50} of crenolanib against the D835Y, TKD mutation of FLT3 was 8.8nM.

Crenolanib is cytotoxic to myeloid leukemia cell lines with FLT3 mutation with concomitant inhibition of FLT3 phosphorylation and its downstream signaling pathways

Crenolanib has been shown to inhibit FLT3 phosphorylation and downstream signaling in both myeloid leukemia cell lines with FLT3-ITD as well as in primary leukemic blasts with FLT3 ITD or TKD mutations.

Metabolic activity as determined in the MTT assay was used to quantitate crenolanib-mediated cytotoxicity in a number of AML cell lines. Crenolanib was determined to be cytotoxic to the FLT3/ITD-expressing leukemia cell lines Molm14 and MV411, at IC50 values of 7 nM and 8 nM, respectively (Figure 4.3).

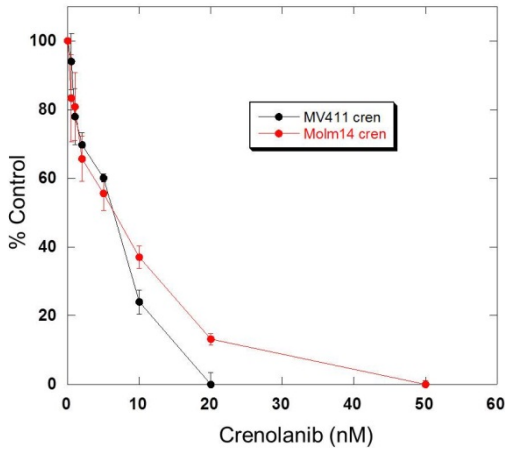


Figure 4.3. In MTT assays, crenolanib is cytotoxic to MV411 and Molm14 cell lines, with IC_{50} values of 8nM and 7nM, respectively.[27]

Cytotoxicity of crenolanib can be attributed to its ability to cause near complete inhibition of phosphorylation of FLT3 and its downstream signaling pathways, demonstrated by p-STAT, p-ERK and p-AKT (Figure 4.4).

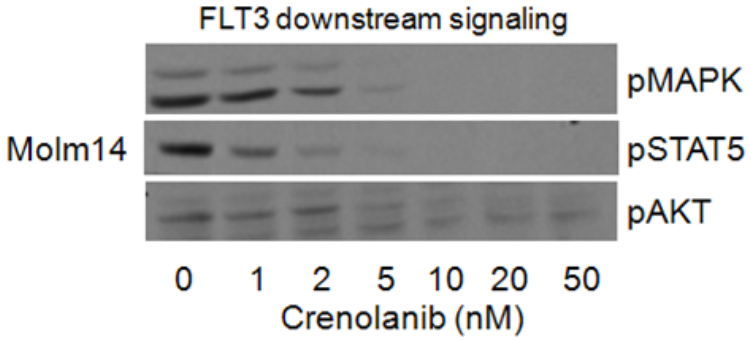


Figure 4.4. Immunoblot experiments performed in Molm14 cells show that crenolanib inhibits downstream signaling of FLT3 at 10nM.[27]

Primary leukemic blasts from AML patients bearing mutant FLT3 are killed at clinically achievable concentrations of crenolanib

The cytotoxic effects of crenolanib were evaluated on blasts isolated from AML patients. MTT assays were performed on AML patient samples procured from the John Hopkins University tumor and tissue bank. These included:

a) A newly diagnosed patient with FLT3/D835 mutation
b) Relapsed, refractory patients with FLT3/ITD AML, who have previously been treated with standard or high dose chemotherapy (N=4)
c) A refractory AML patient with FLT3/D835 who had previously been treated with FLT3 inhibitors (N=1)

Crenolanib has *in vitro* activity against blasts with FLT3-D835 mutation, resistant to both sorafenib and quizartinib

Leukemic blasts from a newly diagnosed patient with the FLT3-D835V mutation were resistant to sorafenib and quizartinib but sensitive to crenolanib. Immunoblotting showed that crenolanib inhibited phosphorylation of mutant FLT3, while quizartinib and sorafenib did not, suggesting the greater in vitro efficacy of crenolanib in this subset of FLT3 mutant AML (Figure 4.5).

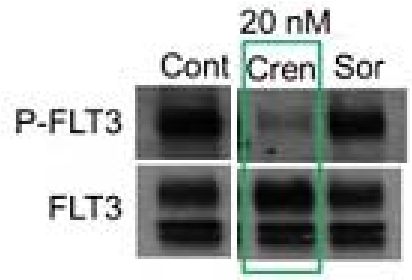


Figure 4.5. Immunoblot experiment performed at 20nM comparing the activity of crenolanib and sorafenib against leukemic blasts with the FLT3-D835V mutation shows that blasts were resistant to sorafenib, while crenolanib provided near complete (>90%) inhibition of phosphorylated FLT3. [27]

Crenolanib is cytotoxic to leukemic blasts from relapsed/refractory AML patients with FLT3/ITD mutation

Crenolanib was evaluated in an MTT assay against leukemic blasts from relapsed/refractory AML patients. Four patient samples were evaluated. Crenolanib was active against all samples with IC_{50} values ranging from 15-40nM (Figure 4.6).

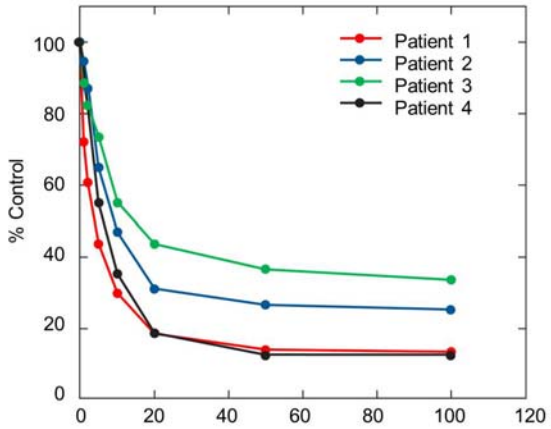


Figure 4.6. Crenolanib was active against all 4 patient leukemic blasts that had the FLT3/ITD mutation.[27]

Crenolanib was active against leukemic blasts from a patient that had progressed on other FLT3 inhibitors including quizartinib and sorafenib

Blasts were obtained from a patient treated with quizartinib and underwent allogeneic transplantation. Following which, the patient relapsed and was treated with sorafenib and quizartinib, with no benefit. Mutational status was determined and it was discovered that there was presence of FLT3/D835 in the background of an FLT3/ITD mutation. In vitro studies demonstrated that crenolanib was highly active against the blasts, at therapeutically achievable concentrations, with an IC_{50} value of 26nM (Figure 4.7).

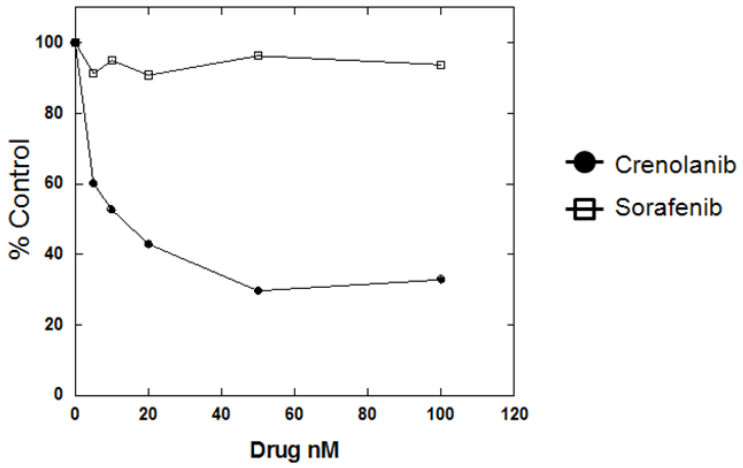


Figure 4.7. Crenolanib was more potent against FLT3 D835 blasts in comparison to sorafenib.[27]

5. CRENOLANIB BESYLATE (CP-868,596-26), CLINICAL DATA

Phase I/II clinical study of oral crenolanib showed that it was well absorbed and well tolerated

Crenolanib has been clinically evaluated as a single agent in a dose-finding and dose-ranging phase-1 study with fifty nine patients treated and was found to have good oral bioavailability. Crenolanib was rapidly absorbed on an empty stomach with a median t_{max} ranging from 1 to 4 hours. The half-life of crenolanib in this Phase I trial was found to be between 13-16 hours.

As of 31 May 2013, no treatment related deaths have been reported in 200 patients treated with crenolanib both as a single agent and in combination. The most frequent non-hematological grade 1/2 toxicities were diarrhea, nausea, and vomiting (Table 5.1). In patients with GIST, anemia was the most frequent grade 1/2 hematological toxicity associated with crenolanib treatment. Four patients required transfusion, though most of these patients had grade 1/2 anemia prior to treatment initiation. The most commonly reported all-causality events of severity Grades 3 or 4 have included LFT increase, anemia, hyponatremia, fatigue and headache.. All LFT abnormalities resolved to baseline or less upon discontinuation of crenolanib. The AML protocol recommends prophylactic antiemetics and anti-diarrheals as well as regular monitoring of hepatic enzymes. Table 5.1 summarizes AEs observed in 126 adult and pediatric patients treated with single agent crenolanib.

Adverse Event	NCI CTC Severity Grade				Total patients = 126	
	GRADE 1	GRADE 2	GRADE 3	GRADE 4	TOTAL AEs	% Patients
Nausea	86	19	2	1	108	63
Vomiting	85	10	4	0	99	55
Diarrhea	62	13	1	0	76	45
Alanine aminotransferase increased	32	9	7	2	50	23
GGT increased	33	14	13	3	63	21
Fatigue	16	12	2	0	30	18
Alkaline phosphatase increased	25	10	2	0	37	14
Anorexia	15	5	1	0	21	13
Aspartate aminotransferase increased	28	11	6	2	47	13
Lymphocyte count decreased	22	10	7	2	41	13
Headache	14	1	2	0	17	10
Anemia	8	6	4	2	20	10
Abdominal pain	11	2	2	0	15	10
Dyspepsia	7	4	2	0	13	10
Dysgeusia	11	3	0	0	14	9
Constipation	11	2	0	0	13	9
White blood cell decreased	16	4	1	0	21	8
Proteinuria	12	0	0	0	12	7
Edema limbs	11	2	0	0	13	6
Hypophosphatemia	10	0	1	0	11	6
Hypoalbuminemia	8	0	0	0	8	6
Periorbital edema	8	0	0	0	8	6
Serum amylase increased	4	3	0	0	7	6
Dizziness	7	0	0	0	7	5
Platelet count decreased	4	0	0	2	6	5

Table 5.1. Incidence of treatment-related AEs occurring in ≥ 5% of the study population treated with single agent crenolanib.

ECG data from patients treated with single agent crenolanib in the phase I trial

Fifty nine patients were treated in the phase I single agent study of crenolanib. ECGs were obtained on all subjects at screening done in triplicate at 2 to 5 minute intervals. Baseline ECG was defined as the closest evaluations prior to the first dose of study drug. The summary of QTc at baseline and on-treatment was provided by overall and dose level for the mean, median, range (minimum, maximum) and the frequencies (n [%] of males with (i) QTc within 431 to 450 msec, (ii) QTc>450 msec; females with (i) QTc within 451 to 470 msec, (ii) QTc>470 msec. Of all subjects examined for ECG at baseline 50.85% had normal values and 49.15% had abnormal value.

Using the Fridericia QTc correction critertia, at baseline, there were no females with >470 msec QTc interval, however 1 male subject reported to have a QTc interval of >450 msec. On study, 4 male subjects had a QTc interval between 431 and 450 msec and 2 female subjects had a QTc interval between 451 and 470 msec. Baseline and worst on study QTc (Fridericia correction) is given in Figure 5.1.

For the Bazett QTc correction, 2 male subjects had a QTc interval >450 msec at baseline and on study 6 male subjects had a QTc interval >450 msec. There were no female subjects with a QTc interval >470 msec at baseline however 1 female subject had a QTc interval >470 msec while on-study. Baseline and worst on study QTc (Bazett correction) is given in Figure 5.1.

Summary of QTc (A. Fridericia correction) Baseline and Worst On-Study Summary of QTc (B. Bazett correction) Baseline and Worst On-Study

A. Treatment Group: Over All

QTc interval (msec)	Baseline (N=59) n	(%)	Crenolanib (CP-868,596) Worst On-Study (N=59) n	(%)
Total (males)	29	(49.2)	29	(49.2)
Mean QTc	400		408	
Median QTc	398		408	
Min QTc	356		370	
Max QTc	459		448	
Total (females)	30	(50.8)	30	(50.8)
Mean QTc	402		411	
Median QTc	400		413	
Min QTc	357		336	
Max QTc	449		457	
431-450 (males)	2	(3.4)	4	(6.8)
451-470 (females)	0		2	(3.4)
>450 (males)	1	(1.7)	0	
>470 (females)	0		0	

B. Treatment Group: Over All

QTc interval (msec)	Baseline (N=59) n	(%)	Crenolanib CP-868,596 Worst On-Study (N=59) n	(%)
Total (males)	29	(49.2)	29	(49.2)
Mean QTc	418		432	
Median QTc	413		428	
Min QTc	365		368	
Max QTc	489		481	
Total (females)	30	(50.8)	30	(50.8)
Mean QTc	425		436	
Median QTc	429		437	
Min QTc	393		374	
Max QTc	460		497	
431-450 (males)	6	(10.2)	8	(13.6)
451-470 (females)	3	(5.1)	9	(15.3)
>450 (males)	2	(3.4)	6	(10.2)
>470 (females)	0		1	(1.7)

Figure 5.1. Summary of QTc (Fridericia correction (A) and Bazett correction (B)) both baseline and worst on-study

There were only two actual grade 1 QT interval prolongations observed in the 59 patients treated, which resolved without need for study drug interruption. No grade 2/3/4 QT interval prolongation has been observed. The grade 1 QT prolongation was observed in 1/6 patients in the 200mg QD without food cohort and in 1/4 patients in the 60mg BID without food cohort. However no QT prolongation was observed in 280mg QD (N=7) and 340mg QD (N=5) without food cohorts and 60 mg BID (N=8) and 100 mg BID (N=12) with food cohorts.

In the pediatric phase I study of crenolanib being conducted at St. Jude's Children Cancer Center (Memphis, TN) in children with gliomas, no episodes of QT prolongations have been observed to date.

No myelosuppression has been observed, as yet, in patients treated with single agent crenolanib

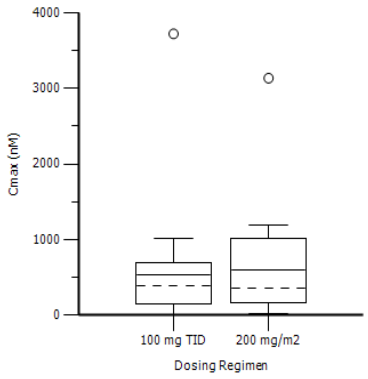
Crenolanib has a K_d for c-kit of 78nM as compared to FLT3 of 0.74nM and could potentially not inhibit c-kit at doses that are adequate to inhibit FLT3. Crenolanib because of its lower affinity for c-kit may have a lower potential to cause delayed marrow recovery in patients with AML. No grade 3/4 myelosuppression has been seen in the adult patients treated to date with crenolanib. In addition, no grey hairs have been observed in any patients treated till-date.

6. RATIONALE FOR DOSE

As of July 1st, 2014, 51 AML patients (combined ARO-004 study and ARO-005 study) have received crenolanib monotherapy . Among these 51 AML patients, the first 26 patients received 100 mg TID and the rest 25 patients received 200 mg/ m2/day. PK parameters are available in all 26 patients at 100 mg TID and in 16 of 25 patients at 200 mg/ m2/day.

PK analysis showed the following: (1) The median planned dose intensity at 200 mg/ m2/day (based on patient BSA) was 340 mg/day (range 300-400mg/day), which is approximately 11% higher than that at 100 mg TID (300 mg/day). (2) The median delivered dose intensity taking all dose reductions and dose delay into account was 314 mg/day (range 214-397 mg/day) at 200 mg/ m2/day and 276 mg/day (range 204-298 mg/day) at 100 mg TID, respectively. (3) The median Day 15 trough level in patients treated with 200 mg/ m2/day were similar to that of patients who received 100 mg TID [median 363 nM (range 40.6-3134) vs. median 419 nM (range 74-3720 nM)]. This suggests that there is no significant difference in median drug exposure among these two dosing groups (Figure 6-2), and more patient convenience within the 100 mg TID.

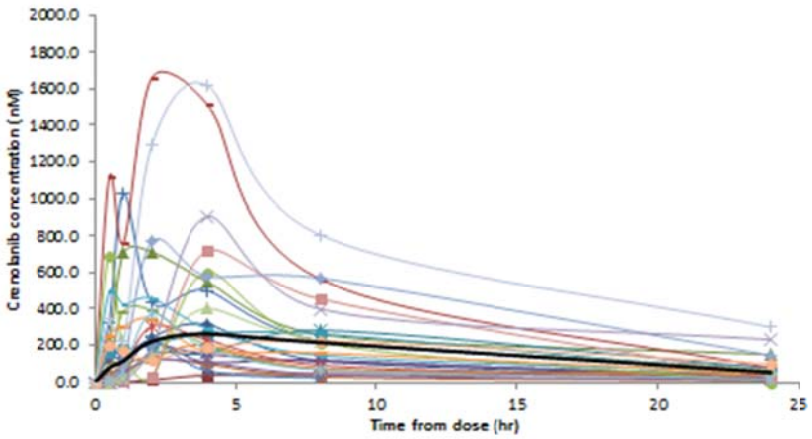
Figure 6-1. Day 15 Crenolanib Trough Levels (100 mg TID and 200 mg/m^2/day)



Thus, a fixed dose regimen of 100 mg TID will be utilized for future clinical studies. Dose reductions to 80 mgTID and 60 mg TID will be applied should certain toxicities emerge in study individuals.

Serum concentrations of crenolanib in AML patients following a single dose of 100 mg is shown in Figure 6-3.

Figure 6-2. Serum Concentrations of Crenolanib following Single Dose (100 mg) in AML Patients



**The median concentration for each time point is depicted by the thick black line.*

7. STUDY DESIGN

This is a Phase II open label study of crenolanib besylate given at 100 mg TID (preferably every eight hours) continuously until one of the criteria for study discontinuation is fulfilled. Study drug 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 IV).

The study will enroll 2 different cohorts of patients in parallel.

Cohort A: Will enroll AML patients with FLT3 activating mutations who have progressed on one or more prior chemotherapy regimen who have not received previously a FLT3 TKI

Cohort B: Will enroll AML patients with FLT3 activating mutations whose leukemia has progressed and have received prior therapy with one or more FLT3 TKIs.

Cycles will be repeated approximately every 28 days, and therapy will be continued until clinically significant disease progression or documentation of unacceptable toxicity as determined by the investigator. If the drug is discontinued for toxicity, patient should be reassessed until toxicity has resolved.

In the setting where hematopoietic stem cell transplant is anticipated study drug will be discontinued at least 72 hours prior to start of conditioning.

Counting Cycle Days: If drug is held or a dose missed, the missed/held dose should not be made up. Dosing will resume with the next scheduled dose. The patient should enter in the diary the doses missed. If drug is held for a day or more, the counting of cycle days should continue as if uninterrupted. The start of cycle 1 is denoted by the ingestion of study drug. The scheduled procedures/visits should comply with the study calendar regardless of amount of study drug administered in a 28 day cycle.

8. PATIENT SELECTION

Patients must have baseline evaluations performed within 14 days prior to the first dose of study drug and must meet all inclusion and exclusion criteria. The exception to this is determination of FLT3 mutation status which can be done within 30 day screening period. 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.

8.1 Inclusion Criteria

1. Confirmed primary with primary AML relapsed or refractory after prior therapy, AML secondary to antecedent chemotherapy or radiation therapy, or AML due to prior myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) as defined by WHO criteria with the presence of either FLT3-ITD and/or other FLT3 activating mutations, whose leukemia has recurred after prior chemotherapy but never received a FLT3 inhibitor (Cohort A) or whose leukemia has progressed after prior therapy and have history of prior exposure to one or more FLT3 TKIs (Cohort B).
2. Patients with secondary AML should have failed no more than two (2) prior cytotoxic chemotherapy containing regimens.
3. Patients with antecedent MDS/MPN defined by WHO criteria, without any prior therapy for AML regardless of the number of therapies for MDS/MPN.
4. Patients with primary AML should have received no more than two (2) prior cytotoxic drug containing salvage regimens. Reinduction with the same regimen or a stem cell transplant following salvage therapy is not considered a separate salvage regimen. Change of drugs will be considered a salvage regimen. Unlimited FLT3 TKI therapy (even in combination with cytotoxics/hypomethylating agents) is allowed for patients enrolled in cohort B.
5. Patients must have tested positive for FLT3-ITD and/or other FLT3 activating mutations within the 30 day screening period.
6. Males and females age ≥18 years
7. ECOG PS 0-2
8. Adequate liver function, defined as bilirubin ≤1.5x ULN, ALT ≤3.0x ULN, and AST ≤3.0x ULN.
9. Adequate renal function, defined as serum creatinine ≤1.5x ULN
10. Recovery from non-hematological toxicities of prior therapy (including HSCT) to no more than grade 1 (except alopecia)
11. Subjects should have received no anti-leukemic therapy except hydroxyurea prior to the first dose of crenolanib as follows: for 14 days for classical cytotoxic agents and for five times the half-life for FLT3 inhibitors and antineoplastic agents that are neither cytotoxic nor FLT3 inhibitors (e.g. hypomethylating agents or MEK inhibitors) Refer to Appendix XVI for half-life information and drugs considered as FLT3 inhibitors for purposes of this trial.

12.

12.1 Negative pregnancy test for women of childbearing potential (WOCBP). WOCBP must practice contraception. Acceptable methods of contraception are double barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, and abstention.

12.2 Male patients with female partners who are of childbearing potential: Recommendation is for male and partner to use effective contraceptive methods, as described above, during the study.

12.3 Women considered not of childbearing potential include any of the following: no menses for at least 5 years or menses within 5 years but amenorrheic for at least 2 months and luteinizing hormone (LH) and follicular stimulating hormone (FSH) values within normal range (according to definition of postmenopausal for laboratory used) or bilateral oophorectomy or radiation castration and amenorrheic for at least 3 months or with bilateral tubal ligation.

13. Able and willing to provide written informed consent.

8.2 Exclusion Criteria

1. Absence of a FLT3 activating mutation
2. <5% blasts in blood or marrow at screening
3. Concurrent chemotherapy, or targeted anti-cancer agents, other than hydroxyurea.
4. Patient with concurrent severe and/or uncontrolled medical conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy.
5. HIV infection or active hepatitis B or C (defined as positive hepatitis B surface antigen positive or hepatitis C antibody positive)
6. Known clinically active central nervous system (CNS) leukemia
7. Patients who are <30 days of a HSCT.
8. Subjects who have clinically significant graft-versus-host disease requiring treatment, and/or have >Grade 2 persistent non hematological toxicity related to the transplant
9. Prior crenolanib treatment for non-leukemic indication
10. Major surgical procedures within 14 days of Day 1 administration of crenolanib.
11. Unwillingness or inability to comply with protocol.

9. TREATMENT PLAN

9.1 General

The study will enroll patients with primary AML relapsed/ refractory after prior therapy, secondary AML (due to prior chemo- or radiation therapy) or prior transformed MDS/MPN with FLT3 activating mutations. Patients will be treated with crenolanib three times daily, preferably every eight hours, continuously until they fulfill one of the criteria for study discontinuation. The objective will be to administer crenolanib at full dose starting at 100 mg TID. Other dose levels will be used for dose adjustments for toxicity (refer to section 10) during therapy. The only exception to this will occur on course 1 day 1, when doses 2 and 3 will be held in order to analyze the pharmacokinetics of the first dose administered out to 24 hours.

Patients currently enrolled at 100mg TID (protocol v1.1) may be dose escalated based on BSA, see table 10.2.

Up to 70 evaluable patients will be enrolled on this study: 30 patients in Cohort A and 40 patients in Cohort B. Patients receiving less than 28 days of study dug will be replaced for efficacy evaluation. All patients will be assessed for toxicity.

9.2 Schedule

Patients will be treated according to the following schedule:

- The starting dose will be 100 mg TID. Dose reductions for adverse events are listed in table 10.2.
- Dose reduction guidelines for adverse events are listed in table 10.2 and 10.3 in Section 10.2. 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.
- One cycle of therapy is defined as 28 consecutive days regardless of whether study drug is taken or not.
- Subsequent cycles may be delayed for recovery of toxicity. Delays in start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after determination of the principal investigator of potential risk/benefit ratio.
- If prolonged (more than 60 days) grade 4 neutropenia or thrombocytopenia with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed, protocol treatment may be interrupted until recovery to ANC $> 0.5 \times 10^9$/L and platelets $>25 \times 10^9$/L . If the peripheral counts do not recover ANC $<0.5 \times 10^9$/L and/or platelets $<25 \times 10^9$/L but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered at the discretion of the investigator.
- For patients who discontinue therapy, the reason for treatment discontinuation will be captured.

9.3 Crenolanib Administration

- Prophylactic antiemetic therapy is recommended to be used as needed for nausea and/or vomiting.
- 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 take the next regular dose at the regularly scheduled time.

9.4 Duration of Therapy

Treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease, or
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
6. Treatment interruption due to toxicity that has not recovered to at least grade 1 within 8 weeks.

It is planned that up to a total of 12 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 12 cycles of therapy may be considered on a case by case basis after discussion with the sponsor's medical monitor.

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. Patients who do not complete one cycle of crenolanib therapy will be replaced. All patients receiving at least one dose of study drug will be considered evaluable for toxicity.

9.5 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, with the exception of hydroxyurea which is allowed for 14 days anytime during the first 28 days on study.

Prophylactic intrathecal therapy is allowed to prevent recurrence of CNS disease. Patients with active CNS disease are excluded.

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

10. DOSING AND DOSE MODIFICATIONS OF CRENOLANIB

Toxicities will be graded using the NCI CTCAE, Version 4.03 (see partial representation in Appendix VII).

The starting dose for all patients will be 100 mg TID.

10.1 Dose Escalation

There will be one level dose escalation allowed for patients who do not experience grade 3 or 4 toxicity and who have no response based on investigator evaluation.

Dose level	Crenolanib dosing
0	100 mg TID
+1	120 mg TID

Table 10.1. Crenolanib dose escalation guidelines

Dose escalation can occur as early as cycle 1 day 15.

10.2 Dose Reductions for Non-Hematologic Toxicities

Dose reductions for non-hematologic toxicities due to crenolanib, will be done according to the schema outlined in Table 10.1.

- Reductions below 60mg TID are not planned; dose reductions beyond those mentioned in this table or different than those specified, should be discussed with the sponsor and documentation justifying the specified dose recorded. If an appropriate dose is not determined, then it will lead to patients' withdrawal from the study drug, in which the patient will stop taking crenolanib, but will still be followed for outcomes.

Dose level	Crenolanib dosing
0	100 mg TID
-1	80 mg TID
-2	60 mg TID

Table 10.2. Crenolanib dose reduction guidelines

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 10.2).

Grade 3 or 4	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (Table 10.2).

Table 10.3. Crenolanib dose reduction guidelines for All Toxicities (except GI (nausea, vomiting and diarrhea)) related to study drug.

Starting dose (dose level 0) for all patients will be 100 mg TID. A maximum of two (2) dose reductions are allowed in a single patient for toxicity management.

10.3 Dose Reductions of Crenolanib for Hematologic Toxicities

Patients with leukemia usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemia. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first cycle of therapy. After this time, treatment interruptions and dose adjustments may be considered according to the following guidelines:

Patients with neutropenia or thrombocytopenia as a consequence of the disease do not require treatment interruptions for myelosuppression. Dose-reductions in these patients should be considered in an individual case and discussed with the medical monitor. The following guidelines can be used for these patients:

- 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.
- If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts, treatment may continue regardless of neutrophil and platelet count with supportive care as needed.
- Patients with pre-cycle counts of neutrophils $<1x10^9$/L and platelets <100 $x10^9$/L and no evidence of residual leukemia, consider holding therapy until recovery of granulocytes to ≥ 1 $x10^9$/L and platelets ≥ 60 $x10^9$/L, then resume at same or 1 lower dose level according to guidelines mentioned in Table 10.2.

10.4 Additional Dose Modifications requiring discussion with Sponsors Medical Monitor

Modification of dose schedules for toxicities other than the above will be allowed within the following guidelines:

- Dose reductions beyond dose level (-2) should be discussed with the sponsor and documentation of the justification recorded.
- Dose adjustments by more than 1 dose level at a time can be considered when judged in the best interest of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be reviewed by the PI and documented in the medical record. Dose re-escalation may be reconsidered.

10.5 Dose Re-escalation

- A patient who has had a dose reduction for any reason may have their dose re-escalated provided the patient has remained free of toxicity requiring dose adjustments for at least 1 month. Escalation will be made by 1 dose-level increments only, and not more frequent than every cycle. Re-escalation cannot exceed the patient's previous highest dose..

10.6 Cycle Delays

- A cycle of therapy may be delayed for a maximum of 8 weeks to allow recovery from toxicities.
- Inability to re-start therapy within 8 weeks after a treatment interruption for toxicity will constitute grounds for removing the patient from protocol.

10.7 Continued Access to Study Drug

At AROG's discretion, patients receiving crenolanib at the time of study closure may continue to receive crenolanib until disease progression or initiation of other therapy. However, if a serious adverse event (SAE) occurs during this time, AROG may request additional information (such as local lab results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

11. AGENT FORMULATION AND PROCUREMENT

11.1 Dose preparation and Storage of Crenolanib

Crenolanib is supplied as 100 mg and/or 20 mg tablets for oral dosing, in 42-count bottles or 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 to the treating physician before starting a new therapeutic cycle to assess treatment compliance. Study drug will be supplied by AROG Pharmaceuticals LLC. Study drug may be packaged by a third party. Clinical trial materials will be labeled according to regulatory and institutional requirements.

12. CORRELATIVE/SPECIAL STUDIES

12.1 Plasma Inhibitory Assay

Sampling Strategy
Samples collected during study of crenolanib therapy will be collected into heparinized (green op) vacutainers and will be transported to the laboratory.

Peripheral blood for plasma inhibitory assay will be drawn pre and post administration of first crenolanib dose on day1 cycle 1 at the following time points: pre dose and at 30 (± 10), 60 (± 15), 120 (± 15) minutes, 4 (±1) hours, 8 (±2), and 24 (±6) hours (Day 2) after crenolanib administration.
In order to obtain the 24-hour time point, all other day 1 dosing (2 doses) will be held. It is also crucial that the 24-hour time point be obtained prior to dose administration on day 2.

Blood samples will also be drawn for plasma inhibitory analysis pre and post administration of first crenolanib dose on day 15 of cycle 1 at the following time points: pre dose, 30 (± 10) minutes, and 4 (±1) hours after administration of first crenolanib dose.
Do not administer second or third dose of crenolanib until after 4 hour timepoint is obtained on day 15 of cycle 1.

On subsequent courses, samples may be obtained at the discretion of the investigator (e.g., pre-dose), and whenever possible every 2-4 cycles. (Appendix V).

Sampling Collection and Processing Instructions for Plasma Inhibitory Assay Analysis

Please refer to the lab manual provided by AROG Pharmaceuticals. The date and time of sample collection, crenolanib dose, and date and time of the last crenolanib dose should be recorded on the appropriate Plasma Inhibitory Assay Data Collection Form (Appendix IX-B, X-B and XI-B)

Sampling Handling and Shipping Instructions

The participating institution will arrange for shipments of samples collected for plasma inhibitory assay for each patient enrolled on the study.

Samples should be shipped within 30 days of the last sample collection. Specimens collected should be shipped via FedEx Priority Overnight shipping for delivery Monday through Thursday. Weekend and holiday deliveries should be avoided. In preparation of sample shipment, contact AROG Pharmaceuticals (refer to appendix XV) and Levis lab (Appendix XIII) to notify of sample shipment and to provide the FedEx tracking number. AROG Pharmaceuticals will confirm shipment from the site. Ship all plasma inhibitors assay samples on dry ice, along with a completed Data Collection Form (Appendix IX-B, X-B and XI-B)

12.2 Pharmacokinetic Assay

Description of the Assay

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 first crenolanib dose Day 1 of cycle 1 at the following time points:
pre dose and at 30 (± 10), 60 (± 15), 120 (± 15) minutes, 4 (±1) hours, 8 (±2) hours, and 24 (±6) (Day 2) hours after crenolanib administration.

In order to obtain the 24-hour time point, all other day 1 dosing (2 doses) will be held. It is also crucial that the 24-hour time point be obtained prior to dose administration on day 2.

Blood samples will also be drawn for pharmacokinetic analysis pre and post administration of first crenolanib dose on day 15 of cycle 1 at the following time points: pre dose, 30 (± 10) minutes, and 4 (±1) hours after administration of the first crenolanib dose.

Do not administer second or third dose of crenolanib until after 4 hour timepoint is obtained on day 15 of cycle 1.

Blood samples will also be drawn for pharmacokinetic analysis pre and post administration of first crenolanib dose on **day 1 of cycle 2** and **day 1 of cycle 3** at the following time points:

- Pre dose
- 4 ±1 hour

Do not administer second or third dose of crenolanib until after 4 hour timepoint is obtained on day 1 of cycle 2 and day 1 of cycle 3.

Peripheral blood sampling for pharmacokinetic assay and bone marrow aspiration for day 1 of cycle 2 should be done on the same day

On subsequent courses, samples may be obtained at the discretion of the investigator (e.g., pre-dose), and whenever possible every 2-4 cycles. (Appendix V).

Sampling Collection and Processing Instructions

Please refer to the lab manual provided by AROG Pharmaceuticals. 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 IX-A, X-A and XI-A).

Sampling Handling and Shipping Instructions

In preparation of shipping samples, contact AROG Pharmaceuticals (refer to appendix XV) and MicroConstants (Appendix XIII) to notify of sample shipment and to provide FedEx tracking number. AROG Pharmaceuticals will confirmation shipment from site.
Samples should be shipped within 60 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. Ship all pharmacokinetic samples on dry ice, along with a completed Pharmacokinetics Data Collection Form (Appendix IX-A, X-A and XI-A).

12.3 Bone Marrow Samples and Other Correlative Studies

Sampling collection schedule:
Prior to start of first dose of crenolanib, a baseline sample of bone marrow or peripheral blood containing blasts should be obtained. If entry bone marrow aspiration was done per eligibility criteria (within 30 days prior to study drug initiation) as part of screening but no aspirate is available at time of enrollment, obtain 1 green top tube of blood and process per bone marrow aspirate instructions in AROG Pharmaceuticals laboratory manual.

It is preferable that bone marrow aspiration for screening baseline evaluation be done within 14 days of start of study drug and a **sample of this marrow should also be shipped as per instructions below.**

Additional bone marrow aspirations (x2) should be taken at the following time points:

- Cycle 2 day 1 +4 days*
- Cycle 3 day 1 ±7 days
- Then every 3 cycles ±1 cycle as long as criteria for CR is maintained.

*bone marrow sampling day 1 cycle 2 should match sampling days for plasma inhibitory assay and pharmacokinetic assay.

Sampling Collection:
Bone marrow aspiration (BMA) will be done as per institutional protocol. Please refer to lab manual provided by AROG Pharmaceuticals for additional information.

Refrigerated BMA samples should be **shipped within 24 hours** of collection along with Data Collection Form.

Shipping of bone marrow samples:

In preparation of marrow sample shipment, contact AROG Pharmaceuticals (refer to appendix XV) and ProPath (Appendix XIII) to notify of sample shipment and provide the FedEX tracking number. AROG Pharmaceuticals will provide confirmation regarding shipment from site. Ship all bone marrow samples on dry ice, along with a completed Data Collection Form (Appendix XII).

At loss of CR, bone marrow biopsy should be performed as clinically indicated to exclude toxicity issues such as persistent pancytopenia due to study drug vs progressive AML. For patients remaining on study drug without significant toxicity for more than 12 months, subsequent evaluations during study may be modified after discussion with the sponsor.

Blood samples will also be drawn for future correlative science research studies at the following two time point's:

- **Pre administration of first dose of crenolanib on day 1 of cycle 1**
- **Day (+14days) at which patient is determined to have progressive disease by the PI**

In preparation of sample shipment, contact AROG Pharmaceuticals (refer to appendix XV) and ProPath (Appendix XIII) to notify of sample shipment and provide the FedEX tracking number. See lab manual/instructions for more details.

Tissue cells and blood samples may be requested for immediate assessment in other tests which assess study drug activity on the biologic targets or samples 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. The total blood drawn for these studies will be less than 400ml in any month.

13. PATIENT EVALUATION

13.1 Pre-Treatment Evaluation

All pretreatment studies should be obtained within 14 days of entry into the trial, unless otherwise stated.

1. Medical history (includes documentation of current medications and allergies)
2. Height, weight, vital signs
3. Physical examination with baseline laboratory tests
4. ECOG Performance Status (Appendix III)
5. Serum or urine pregnancy test for women of child bearing capacity
6. A complete history and physical, documentation of all disease, concomitant medications and performance status
7. CBC, platelet count, differential (differential may be omitted if WBC is $<0.5 \times 10^9$/L)
8. Creatinine, total bilirubin, ALT, and AST
9. HIV infection or hepatitis B or C screening. (positive defined as hepatitis B surface antigen positive or hepatitis C antibody positive)
10. Bone marrow aspirate during the last 30 days preceding study initiation is acceptable for study entry as long as blast count is available from that marrow. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose, if done within 6-months of enrollment)
11. Evaluation of FLT3 mutation status (if not done < 30 days of start of study drug).
12. Peripheral blood for optional procedures

* Every effort will be made to collect optional procedures at all 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.

13.2 Evaluation during Treatment

1. Physical exam at the start of each cycle (± 4 days) for the first 2 cycles, then every 2 cycles and documentation of all concomitant medications.
2. CBC, platelet count, differential (differential may be omitted if WBC is $<0.5 \times 10^9$/L) twice weekly (at least 24 hours apart) for the first two weeks of cycle 1, once weekly (± 3 days) for the second two weeks of cycle 1, bi-weekly (± 4 days) for the second cycle and once a month thereof from cycle 3 until cycle 12 (± 14 days).
3. Creatinine, total bilirubin, ALT, AST, twice weekly (at least 24 hours apart) for the first two weeks of cycle 1, once weekly (±3 days) for the second two weeks of cycle 1, bi-weekly (± 4 days) for the second cycle and once a month thereof from cycle 3 until cycle 12 (± 14 days).
4. Bone marrow aspiration x 2 should be taken at these timepoints: cycle 2 day 1 (+4 days) , then cycle 3 day 1 (+/- 7 days), then every 3 cycles (+/- 1 cycle) as long as criteria for CR is maintained. At loss of CR, bone-marrow aspiration would be performed only as clinically indicated to exclude toxicity issues like persistent pancytopenia due to study drug vs from progressive AML.

5. Peripheral blood for correlative studies will be drawn on day1 at the following time points: pre dose and at 30 (± 10), 60 (± 15), 120 (± 15) minutes, 4 (±1) hours, 8 (±2), and 24 (±6) hours after crenolanib administration. Blood samples will also be drawn on day 15 of cycle 1 at the following time points: pre dose, 30 (± 10) minutes, and 4 (±1) hours after crenolanib administration. Blood samples will also be drawn on day 1 cycle 2 (±2 days), day 1 cycle 3 (±2 days) at the following time points: pre dose, 4 ±1 hours after crenolanib administration. On subsequent courses, samples may be obtained at the discretion of the investigator, pre-dose, and whenever possible every 2-4 cycles.
6. For patients that remain on study with no significant toxicity for more than 12 months, subsequent evaluations during study may be modified after discussion with the sponsor. These may include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), correlative studies to every 6-12 months (or suspension of sample collection for correlative studies), and other laboratory tests to once every cycle.

* Every effort will be made to collect optional procedures at all 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.

Labs obtained with the local physician can be used for monitoring; PI must review and sign source documents within 24 hours of performance of lab at local physician's office unless performed on a Friday in which case review on the following Monday is acceptable. It is encouraged that labs be performed on Monday thru Thursday.

14. CRITERIA FOR RESPONSE

Response criteria will be modified from the International Working Group for AML.[27] Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

14.1 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

14.2 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

14.3 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

14.4 Morphologic Leukemia-Free State:

- Bone marrow: ≤5% myeloblasts

14.5 Hematologic Improvement (HI):

Hematologic response must be described by the number of positively affected cell lines.

- **Erythroid response (E)** (pretreatment Hgb <11 g/dL)
  Hgb increase by ≥1.5 g/dL
- **Platelet response (P)** (pretreatment platelets <100 $x10^9$/L)
  Absolute increase of ≥30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
  Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
- **Neutrophil response (N)** (pretreatment ANC <1.0 $x10^9$/L)
  At least 100% increase and an absolute increase > 0.5 x 10^9/L
- **Blast response (B)**
  At least a 50% reduction in blast percentage in peripheral blood (if > 5%) or bone marrow

15. ADVERSE EVENT REPORTING

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 this 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.

15.1 Adverse Event Reporting

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

For clarity the information required by the sponsor at baseline is to be captured in the CRFs is:

Forms Title	Content to be captured
'Relevant Medical History' (SC_5_Screening)	Any prior important medical history
'Physical Examination' (SC_6_Screening)	From physical examination during screening
'Baseline Medical history' (SC_7_Screening)	Any current medical history
'Baseline Symptoms' (SC_8_Screening)	Any current symptoms

Table 15.1. Sponsor-Required Baseline Information in CRFs.

Adverse Events (AEs) will be evaluated according to the latest CTCAE version 4.03 and documented in medical record. Principal investigator should review and provide documentation of all baseline comorbidites related to the preexisting conditions and/or current medications prior to initiation of cycle one. These events will not be considered as related to crenolanib treatment. If these events continue during the treatment phase they do not need to be captured in the case report form. Captured AEs include:

1) **Any new AE regardless of its grade or expectedness post study drug initiation**
2) **Worsening of any expected or unexpected AEs determined by the principal investigator as related to crenolanib**

Expected events during leukemia therapy are (all other are considered unexpected and should be captured for reporting as outlined above):

1) Febrile or infection episodes
2) Coagulation abnormalities
3) Epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage
4) Preexisting side effects related to prior disease specific therapy or ongoing medications for management of non-leukemia conditions
5) Myelosuppresion and myelosuppression-related events (due to disease)
6) Bone, joint, or muscle pain
7) Fatigue/malaise
8) Weakness
9) Shortness of breath
10) Nausea and vomiting
11) Anorexia
12) Electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)
13) Chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
14) Coagulation abnormalities
15) Alopecia

General Therapy Related Events:

1) Catheter related events (thrombosis, bleeding, infection)
2) Renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy
3) Rash related to antibiotic use
4) Hospitalization for the management of any of the above expected events

Reporting Hematology and Blood Chemistry Results:

- Hematology and blood chemistry results for every scheduled visit or for the most contiguous to the scheduled visit should be reported on case report form.Data captured in addition to the protocol specified scheduled visit is to be captured, only if any abnormal hematological or chemical values resulted in dose modification or dose delay.
- 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.
- If patients goes on to another clinical study or standard therapy, if possible, adverse events should continue to be captured for 30 days, including 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

15.2 Serious Adverse Event (SAE) Reporting:

A serious adverse event 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 be reported to the sponsor as SAE and follow SAE reporting requirements

- 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 event that occur after the 30 day 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.

15.3 Reporting 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.

16. STATISTICAL CONSIDERATIONS

16.1 Determination of Sample Size

The primary endpoint of the study is the overall response rate to crenolanib. The outcome may be different for patients with or without the previous FLT3 TKI therapy. Therefore, patients will be stratified according to whether they have recurred after prior chemotherapy without a FLT3 TKI treatment or they have progressed after prior therapy with a FLT3 TKIs.

Based on the promising results observed to date, the sample size for each cohort will be expanded to include a total of 30 patients in Cohort A and 40 patients in Cohort B. Such additional patients will permit a more accurate assessment of the efficacy and safety of crenolanib in these populations. The total sample size for the two cohorts is 70 patients.

Cohort B (N=40): Two parallel Simon minimax two-stage Phase II designs will be used for the two cohorts of patients. For the patients who progressed after prior chemotherapy with FLT3 TKI, the null response rate will be 5%, and target response rate will be 20%. With alpha of 0.05 and beta of 0.08, the first stage will require 28 patients. If there is 1 or no patient responding, the trial will be stopped. If 2 or more out of the first 28 patients respond, accrual will continue until a total of 40 patients have been enrolled. At the end of the study, if 5 or more patients out of 40 respond, the regimen will be considered active. With this design, the probability of early termination is 59% if the true response rate is only 5%.

Cohort A (N=30): For the patients who progressed after prior chemotherapy without FLT3 TKI, the null response rate will be 5%, and target response rate will be 30. With alpha of 0.06 and beta of 0.01, the first stage will require 24 patients. If there is 1 or no patient experiencing the response, the trial will be stopped. If 2 or more out of the first 24 patients respond, accrual will continue until a total of 30 patients have been enrolled. At the end of the study, if 4 or more patients out of 30 respond, the regimen will be considered active. With this design, the probability of early termination is 66% if the true response rate is only 5%.

The method of Thall, Simon, and Estey will be employed to perform interim safety monitoring. We will assume a Beta (0.6, 1.4) prior distribution for the toxicity rate which in particular has mean of 30%. The toxicity is defined as any grade 3 or greater non-hematologic toxicities attributed to the study drug.

The following decision criteria will be applied continuously up to the 70 patient. The two cohorts of patients will be jointly monitored for the safety. Targeting a 30% toxicity rate as a trade-off, the trial will be stopped early according to the following monitoring rule.

$$\Pr\{\text{toxicity rate} > 30\% | \text{ data}\} > 0.93$$

That is, if at any time during the study we determine that there is more than a 93% chance that the toxicity rate is more than 30% we will stop the study.

The design software Multc Lean Desktop (version 2.1) developed by the Department of Biostatistics at M. D. Anderson Cancer Center (MDACC) was used to generate the toxicity stopping boundaries and the OC table. The stopping rule boundary is shown in table 16.1.

Table 16.1 Safety monitoring boundary

#patient	Stop the trial if there are this many toxicities total:
5	4-5
10	6-10
15	8-15
20	10-20
25	12-25
30	14-30
35	15-35
40	17-40
45	19-45
50	21-50
55	22-55
60	24-60
65	26-65

The operating characteristics of this rule in the trial are shown in the following table

Table 16.2 The operating characteristics

True toxicity	Early Stopping Probability	Average number of patients treated
0.2	0.02	69.1
0.25	0.06	67.0
0.3	0.18	61.8
0.35	0.42	52.2
0.4	0.71	39.9
0.5	0.98	20.4

16.2 Toxicity Evaluation

Crenolanib has been well tolerated in studies including over 100 patients and toxicity patterns are relatively well understood.

16.3 Statistical and Analytical Plans

The primary end-point is overall response rate. The overall response rates in the two cohorts will be evaluated along with its 95% confidence interval. Analysis of secondary endpoints will be predominantly descriptive statistics and will be interpreted as being exploratory and hypothesis generating. Progression free survival (PFS) and overall survival (OS) will be estimated using the method of Kaplan-Meier. Cox regression models will be used to determine the relationship with the time-to-events (e.g. PFS and OS) and the potential prognostic factors. Exploratory logistic regression will be used to identify the prognostic factors that are significantly correlated with the response rate.

16.4 General Considerations

Statistical analysis of this study will be the responsibility of AROG Pharmaceuticals or its designees. The clinical research physician/scientist and statistician will jointly be responsible for the appropriate conduct of an internal review process for the final study report and any study-related material to be authorized for publication by AROG or its designees.

Safety endpoints will be reported with descriptive statistics for overall study population. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Patient Disposition

A detailed description of patient disposition, broken by cohort, will be provided. It will include:

- Summary of patients entered
- Total number of patients entered
- Total number of patients enrolled
- Summary of reasons for patients entered, but not enrolled
- Summary of reasons for patient discontinuation from study treatment
- Summary of all identified important protocol violations

Patient Characteristics

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

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions

- Prior therapies

Other patient characteristics will be summarized as deemed appropriate.

Concomitant Therapy

Concomitant medication will be reported at each visit with start/stop dates. If warranted, an attempt may be made to determine how concomitant medications are related to observed study outcomes.

Treatment Compliance

Treatment compliance information will be collected through pill counts at each tumor assessment visit and also by analyzing patient diaries where patients will record their daily drug intake. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual number of pills taken}}{\text{Number of pills expected to be taken}} \times 100$$

The number of tablets taken will be determined by counting the number of tablets returned at each visit and subtracting that number from the number of tablets dispensed. The number of tablets expected to be taken will be determined by the assigned dose and taking into account any prescribed dose reductions and omissions.

No minimal level of compliance will be defined for patient inclusion in efficacy analyses. An exploratory analysis of compliance may be performed by regressing percent compliance on selected efficacy endpoints. If significant results are indicated, analysis may be performed to determine the level of compliance that best delineates each endpoint.

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 patients are continuing to benefit from study treatment, they will be allowed to continue receiving study treatment. If patients continue on crenolanib beyond study closure, safety data must be collected. If further data are collected that are not included as part of the final locked database, the post hoc data will eventually be combined with the locked database and stored in a data library separate from the locked database.

17. 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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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 MD Anderson internal form can be used.

I. Study Information

Protocol Title:	A Phase II Study of Crenolanib in Acute Myeloid Leukemia Patients with FLT3 Activating Mutations
Protocol Number:	ARO-005

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria:Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. Confirmed primary AML relapsed or refractory after prior therapy, AML secondary to antecedent chemotherapy or radiation therapy, or AML due to MDS/ MPN as defined by WHO criteria with presence of FLT3 ITD and or/other FLT3 activating mutations, whose leukemia has recurred after prior chemotherapy but never received a FLT3 inhibitor (Cohort A) or whose leukemia has progressed after prior therapy and have history of prior exposure to one or more FLT3 TKIs (Cohort B).	☐	☐		
2. Patients with secondary AML who have failed no more than two prior cytotoxic chemotherapy containing regimens.	☐	☐	☐	
3. Patients with antecedent MDS/MPN, defined by WHO criteria, without any prior therapy for AML, regardless of the number of therapies for MDS/MPN.	☐	☐	☐	

4. Patients with primary AML with no more than two prior cytotoxic drug containing salvage regimens. Reinduction with the same agents is not considered a salvage regimen. Change of drugs will be considered a salvage regimen. Unlimited FLT3 TKI therapy (even in combination with cytotoxics/hypomethylating agents) is allowed for patients enrolled in cohort B.	☐	☐	☐	
5. Positive for AML with FLT3-ITD and/or other FLT3 activating mutations as tested within 30 days of enrollment.	☐	☐		
6. Age ≥18 years	☐	☐		
7. ECOG Performance Status 0 - 2	☐	☐		
8. Liver function: ALT ≤ 3.0x ULN AST ≤ 3.0x ULN Bilirubin ≤ 1.5x ULN	☐	☐		
9. Serum creatinine ≤ 1.5x ULN	☐	☐		
10. Recovery from toxicities of prior therapy (including HSCT) to no more than grade 1 (except alopecia)	☐	☐		
11. Subjects should have received no anti-leukemic therapy (except hydroxyurea) for 14 daysfor classical cytotoxic agents and for five times the half life of FLT3 inhibitorsprior to first dose of crenolanib and antineoplastic agents that are neither cytotoxic nor FLT 3 inhibitors.	☐	☐		
12. Negative pregnancy test for women of childbearing potential	☐	☐		
13. Able and willing to provide written informed consent	☐	☐	☐	

Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. Absence of FLT3 activating mutation	☐	☐		
2. <5% blasts in blood or marrow at screening (i.e. only extra-medullary leukemia)	☐	☐		
3. Concurrent chemotherapyor targeted anti-cancer agents, other than hydroxyurea.	☐	☐		
4. Patient with concurrent severe and/or uncontrolled medical conditions that in the opinion of the investigator may impair the participation in the study or the evaluation of safety and/or efficacy	☐	☐		
5. HIV infection or active hepatitis B or C	☐	☐		
6. Known clinically active central nervous system (CNS) leukemia	☐	☐		
7. Subjects who are <30 days of an HSCT.	☐	☐	☐	
8. Subjects who have clinically significant graft-versus-host disease requiring treatment, and/or have >Grade 2 persistent non hematological toxicity related to the transplant	☐	☐	☐	
9. Prior crenolanib treatement for a non-leukemia indication	☐	☐	☐	
10. Major surgical procedures within 14 days of Day 1 administration of crenolanib	☐	☐	☐	
11. Unwillingness or inability to comply with protocol	☐	☐	☐	

*****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. ECOG Performance Status Criteria

Performance Status Criteria	
ECOG (Zubrod)	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory, and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair

Appendix IV. 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 - 005

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 - 005

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 - 005

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 besylate (CP-868,596-26)

Protocol ID: ARO - 005

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 V. Study Schedule

	screening	Therapy									End of Study visit	Follow-up visit
Cycle No.		1					2		3	n		
Duration		28d					28d		28d	28d		
Relative day within cycle	(-)14	1	2	8	15	22	1	15	1	1		
Informed Consent	X											
Inclusion/Exclusion	X											
Demography	X											
Relevant medical history, current medical conditions including AML-specific history	X	X										
Evaluation of FLT3-D835, FLT3-ITD, and other mutational status	X											
Height	X											
Prior/Concomitant medications, significant non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[1]	X	X					X		X	X	X	X
Vitals, ECOG Performance Status, Weight	X	X		X	X	X	X	X	X	X	X	X
AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests												
Hematology[2]	X	X X		XX	X	X	X	X	X	X	X	X
Serum Chemistries[2]	X	XX		XX	X	X	X	X	X	X	X	X
HIV, HepB/C	X											
Urine or serum Pregnancy test	X										X	
Peripheral blood for PK analysis[3]		X	X		X		X		X			
Peripheral blood for correlative analysis[3]		X	X		X							
Disease assessment												
Bone marrow aspirations (x2)[4]	X	X					X		X	X		

[1]Physical examination = .Day 1 +/- 4 days

[2] CBC includes platelet count, differential (differential may be omitted if WBC is <0.5 x10^9/L), Chemistry panel including AST, ALT, and total bilirubin to be drawn twice weekly (at least 24 hours apart) for the first two weeks of

cycle 1, once weekly (± 3 days) for the second two weeks of cycle 1, bi-weekly (± 4 days) for the second cycle and once a month thereof from cycle 3 until cycle 12 (± 14 days).

Labs obtained with the local physician can be used for monitoring; PI must review and sign source documents within 24 hours of performance of lab at local physician's office unless performed on a Friday in which case review on the following Monday is acceptable. It is encouraged that labs be performed on Monday thru Thursday.
At the time of any dose escalation, labs should be drawn twice per week for at least one week.

[3]Peripheral blood for translational research and correlative analysis including Pharmacokinetics Assay and Plasma Inhibitory Assay will be obtained at multiple time points on Day 1 of Cycle 1, the 24 hour drug level would be obtained on Day 2 of Cycle 1. Samples will also be obtained at multiple time points on Day 15 of Cycle 1, Day 1 of Cycle 2, and Day 1 of Cycle 3. Further collections may be as requested by sponsor. Additional samples may be drawn at the discretion of the investigator. At the time of any dose escalation, labs should be drawn twice per week for at least one week.

[4]Baseline bone marrow aspirations (two aspirates at each time point, see section 12.3) or a sample of peripheral blood containing blasts should be collected prior to start of crenolanib therapy. Ideally, entry bone marrow should be done within 14 days of Cycle 1 Day 1 (baseline.), however a marrow done within 30 days of enrollment is allowed if baseline blast count can be assessed. Additional aspirations should be taken at cycle 2 day 1 (+ 4 days), cycle 3 day 1 (+/- 7 days), then every 3 cycles (+/- 1 cycle) as long as criteria for CR is maintained. At loss of CR, bone-marrow biopsy would be performed only as clinically indicated to exclude toxicity issues (such as persistent pancytopenia due to study drug vs from progressive AML.)

Appendix VI. Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils, segmented	Direct bilirubin
Lymphocytes	Indirect bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Alanine aminotransaminase (ALT/SGPT)
Basophils	Aspartate aminotransferase (AST/SGOT)
Platelets	Gamma-glutamyltransferase (GGT)
	Blood urea nitrogen (BUN)
	Creatinine
	Phosphorus
	Calcium
	Glucose, random
	Albumin
	Lactate dehydrogenase
	Pregnancy Test (serum or urine; females only)[a,c,d]

Abbreviations: RBC = red blood cells, WBC = white blood cells.

a Performed by local lab

b Local Lab results may be used for enrollment or dosing decisions

c Required for women of childbearing potential. Women are considered not of childbearing potential if they are surgically sterile or are postmenopausal. Patients may be entered and enrolled on the basis of a local serum or urine pregnancy test

d Repeat test as clinically indicated

e Repeat test on Day 1 of each cycle of therapy.

Note: Patients may be enrolled on the basis of local chemistries.

Investigators must document their review of each lab report.

Appendix VII. Common Terminology Criteria for Adverse Events (CTCAE); Version 4.03

Investigations					
	Grade				
Adverse Event	1	2	3	4	5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					

Appendix VIII. 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 IX-A. ARO-005 C1D1 Pharmacokinetic Data Collection Form

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

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 Day 1 crenolanib dose. Use an additional sheet if necessary.

_____
_____
_____

Fill in crenolanib dose date, time, and tolerance in the spaces below. ***HOLD SECOND AND THIRD DOSE of crenolanib on day 1. Obtain 24 hour sample prior to administration of crenolanib doses on day 2.*** 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 Samples	Date	Scheduled Time	Actual Time
Prior to crenolanib dose (pre)			
30 (± 10) minutes after dose			
60 (± 15) minutes after dose			
120 (±15) minutes after dose			
4 (±1) hours after dose			
8 (±2) hours after dose			
24 (±6) hours after dose (C1D2)			

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

Appendix IX-B. ARO-005 C1D1 Plasma Inhibitory Assay Data Collection Form

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

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 Day 1 crenolanib dose. Use an additional sheet if necessary.

_____

_____

_____

Fill in crenolanib dose date, time, and tolerance in the spaces below. ***HOLD SECOND AND THIRD DOSE of crenolanib on day 1. Obtain 24 hour sample prior to administration of crenolanib doses on day 2.*** 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 Samples	Date	Scheduled Time	Actual Time
Prior to crenolanib dose (pre)			
30 (± 10) minutes after dose			
60 (± 15) minutes after dose			
120 (±15) minutes after dose			
4 (±1) hours after dose			
8 (±2) hours after dose			
24 (±6) hours after dose (C1D2)			

Name of person completing form: _____

Phone Number: _____

Email: _____

Date: _____

Appendix X-A. ARO-005 C1D15 Pharmacokinetic Data Collection Form

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

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 Day 15 crenolanib dose. Use an additional sheet if necessary.

_____
_____
_____

Fill in *exact* dose dates, times, and tolerances for the *prior 4* crenolanib doses in the spaces below.

Crenolanib Date Administered	Time Administered	Crenolanib Tolerance

List the scheduled and actual times of the pharmacokinetic samples in the chart below. List exact date and time of day 15 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. ***Note: Do not administer second or third crenolanib dose until after 6 hour sample is collected.***

Cycle 1 Day 15 Samples	Date	Scheduled Time	Actual Time
Prior to Day 15 crenolanib dose			
30 (±10) minutes after dose			
4 (± 1) hours after dose			

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

Appendix X-B. ARO-005 C1D15 Plasma Inhibitory Assay Data Collection Form

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

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 Day 15 crenolanib dose. Use an additional sheet if necessary.

_____
_____
_____

Fill in *exact* dose dates, times, and tolerances for the *prior 4* crenolanib doses in the spaces below.

Crenolanib Date Administered	Time Administered	Crenolanib Tolerance

List the scheduled and actual times of the pharmacokinetic samples in the chart below. List exact date and time of day 15 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. ***Note: Do not administer second or third crenolanib dose until after 6 hour sample is collected.***

Cycle 1 Day 15 Samples	Date	Scheduled Time	Actual Time
Prior to Day 15 crenolanib dose			
30 (±10) minutes after dose			
4 (± 1) hours after dose			

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

Appendix XI-A. ARO-005 C__D__ Pharmacokinetic Data Collection Form

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

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 *exact* dose dates, times, and tolerances for the *prior 4* crenolanib doses in the spaces below.

Crenolanib Date Administered	Time Administered	Crenolanib Tolerance

List the scheduled and actual times of the pharmacokinetic 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. ***Note: Do not administer second or third crenolanib dose until after 6 hour sample is collected.***

Samples	Date	Scheduled Time	Actual Time
Prior to crenolanib dose			
4 (± 1) hours after dose			

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

Appendix XI-B. ARO-005 C__D__ Plasma Inhibitory Assay Data Collection Form

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

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 *exact* dose dates, times, and tolerances for the *prior 4* crenolanib doses in the spaces below.

Crenolanib Date Administered	Time Administered	Crenolanib Tolerance

List the scheduled and actual times of the pharmacokinetic 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. ***Note: Do not administer second or third crenolanib dose until after 6 hour sample is collected.***

Samples	Date	Scheduled Time	Actual Time
Prior to crenolanib dose			
4 (± 1) hours after dose			

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

Appendix XII. Bone Marrow Aspiration: Data Collection Form (Baseline / C_D_)

Study Acc #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA:
Crenolanib Dose(mg):	Crenolanib Dosage (mg/m^2):	Today's Date:

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

Dateof Dose: _____
Dose Administration Time: _____
Describe Dose Tolerance: _____

Bone Marrow Aspiration	Actual Time	Sample Volume or Estimated Mass	Note any collection issues
Sample – 1			
Sample – 2			

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

Appendix XIII. 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. Plasma Inhibitory Assay Samples

Mark Levis, MD PhD
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital
Cancer Research Building 1, Room 230
1650 Orleans Street
Baltimore, MD 21231
(410) 955-8964
LevisMa@jhmi.edu

C. Bone Marrow Aspirate Samples

Debrah Cohen
Cytogenetis and Molecular Laboratory Manager
ProPath
1355 River Bend Drive
Dallas TX 75247
214.237.1739
Fish@propath.com
www.ProPath.com

Appendix XIV. CYP3A4 Inducing or Inhibiting Drugs with the Potential to Affect 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)
oxcarbamazepine (anticonvulsants and mood stabilizers)	ketoconazole (azole antifungals)
phenobarbital (barbiturates)	itraconozole (azole antifungals)
rifampicin (bactericidal)	Posaconazole (azole antifungals)
modafinil (stimulant)	Voriconazole (azole antifungals)
dexamethasone	
hyperforin (constituent of St. John's Wort)	nefadozone (antidepressant)
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)

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix XV. Contact Information of Arog Pharmaceuticals

Contact Information of Medical Monitor

Nora Ku, M.D.
Telephone: 305.283.5896
E-mail: nku@arogpharma.com

Contact Information of Study Manager

Abhijit Ramachandran
AROG Pharmaceuticals, LLC
E:aramachandran@arogpharma.com
O: 214.593.0515
M: 817.849.0175
F: 214.594.0002

Contact Information of Study Monitors

Pritam Kambuj
AROG Pharmaceuticals, LLC
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M: 214.593.0512

Contact Information for notification of shipment of correlative studies samples

Justin Rains
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E: jrains@arogpharma.com
O: +1 214.593.0500
M: +1 817.849.0175
F: +1 214.594.0002

Appendix XVI. FMS-like Tyrosine Kinase 3 Inhibitors Currently Being Studied in the Treatment of Leukemia and Their Half-life

Following are few examples of FLT3 inhibitors and their half-lives based on current available data:

Trade name	Compound	Half-life	5X Half-life	Days
Dovitinib	TKI258	18 hours	90 hours	4
KW-2449*	KW-2449	3.5 hours	17.5 hours	1
Lestaurtinib	CEP-701	9.2 hours	46 hours	2
Midostaurin	PKC412	38.4 hours	192 hours	8
PLX3397*	PLX3397	20 hours	100 hours	4
Quizartinib	AC220	36 hours	180 hours	8
R406*	R406	15 hours	75 hours	3
Sorafenib	BAY-43-9006	27 hours	135 hours	6
Sunitinib	SU11248	86 hours	430 hours	18
Tandutinib	MLN518	33 hours	165 hours	7

**No trade name is currently available*