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

Version 4.0

Confidential Information

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- Overall response rate defined as Complete remission (CR) including incomplete blood count recovery (CRi)
- Duration of response
- Progression-free survival

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- Pharmacokinetic analysis of crenolanib in patients with AML
- Analysis of phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples
- Pharmacogenetic analyses, correlation of remission with genomic abnormalities including but not limited to mutant FLT3 allelic ratio
- Impact of crenolanib on hematological improvement, bridge to transplant, duration of leukemia control, blood and platelet transfusions, infections, days of hospitalization, performance status

2. Sponsor Contact Information

Protocol Number:	ARO-004
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Development Phase:	II
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3. Synopsis

Study Rationale

A number of FLT3 inhibitors with *in vitro* and *in vivo* activity against the FLT3 internal tandem duplication (ITD) mutation are in clinical development. These include midostaurin (PKC412, in phase III development), sorafenib (in phase III development), and quizartinib (AC220, in phase II development).

However, most AML patients who initially respond to these FLT3 tyrosine kinase inhibitors (TKIs) relapse. One of the mechanisms of resistance to FLT3 inhibitors is the development of secondary mutations in the FLT3 tyrosine kinase domain (TKD). The most common secondary TKD mutations that have been identified are substitutions of aspartic acid at the position 835 of FLT3 (D835Y/V). The D835 substitution mutation in FLT3 results in ligand-independent constitutive phosphorylation of the tyrosine residues present in the kinase domains of FLT3 protein. This mutation is resistant to midostaurin, sorafenib and even quizartinib. Thus, there exists a need to develop FLT3 inhibitors with the ability to inhibit FLT3-D835 signaling to treat patients with relapsed AML.

Crenolanib besylate (CP-868,596-26) is an orally bioavailable benzimidazole that was designed to be a selective and potent inhibitor of type III receptor kinases FLT3, PDGFRα and PDGFRβ. Crenolanib not only inhibits the wild type FLT3, but also its constitutively active mutations. In vitro studies have shown that Crenolanib has a high affinity for mutant FLT3 with K_d values of 0.43nM. In addition, crenolanib has high affinity for TKD mutations D835H at 0.4nM K_d in contrast to that of 3.7nM for quizartinib and K_d of 30nM for sorafenib, and for D835Y at 0.18nM and known to cause resistance to quizartninb with a K_d of 7.1nM and K_d of 82nM for sorafenib. This high affinity of crenolanib allows it to inhibit aberrant FLT3 signaling at clinically achievable concentrations in AML patients. Crenolanib was able to inhibit phosphorylation of FLT3-D835Y transfected in Ba/F3 cells, with an IC_{50} of 8.8nM.

This activity of crenolanib against both wild type as well as mutant FLT3 has been confirmed in primary AML blast obtained from patients. In these assays, crenolanib was found to be cytotoxic to leukemic blasts with FLT3 activating mutations with concurrent inhibition of FLT3 phosphorylation and downstream signaling pathways like AKT and STAT. The potential ability of crenolanib to overcome resistance developed by patients treated with other FLT3 inhibitors has been assessed by exposing leukemic blasts from patients whose AML had progressed on other FLT3 inhibitors including quizartinib and sorafenib. These leukemic blasts had not only the ITD of FLT3 but also FLT3-D835 mutation. Crenolanib was able to inhibit FLT3 phosphorylation in these blasts as well as inhibit MTT metabolism by these leukemic blasts.

These data suggest that crenolanib could potentially provide therapeutic benefit to the patients with activated FLT3, whether due to ITD or due to TKD mutations like D835, which could be present at the time of diagnosis or be acquired secondary to exposure to other FLT3-TKIs.

This pilot Phase II study is designed to evaluate the efficacy and tolerability of oral crenolanib besylate in patients with relapsed Acute Myeloid Leukemia with FLT3 activating mutations as retreatment of relapsed/refractory AML and in maintaining remission after allogeneic stem cell transplant.

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

Title of Study: A Phase II Study of Crenolanib Besylate in Subjects with Relapsed/Refractory Acute Myeloid Leukemia with FLT3 Activating Mutations

Number of Planned Subjects:
14 evaluable subjects

Length of Study: 3 years

Objectives:

Primary Objectives
- Overall response rate including Complete remission (CR) including incomplete blood count recovery (CRi)
- Duration of response
- Progression-free survival

Secondary Objectives:
- Safety and tolerability of crenolanib
- Pharmacokinetic analysis of crenolanib in patients with AML
- Analysis of phospho-FLT3 and other pharmacodynamic markers from serially collected circulating leukemic blasts and/or marrow blast samples
- Pharmacogenetic analyses, correlation of remission with genomic abnormalities including but not limited to mutant FLT3 allelic ratio
- Impact of crenolanib on hematological improvement, bridge to transplant, duration of leukemia control, blood and platelet transfusions, infections, days of hospitalization, performance status

Study Design:

This is a Phase II open label study of crenolanib besylate. This study will enroll subjects with relapsed or refractory AML with FLT3 activating mutations. Prior treatment with other FLT3 TKIs is allowed. Subjects will take crenolanib 200mg/m^2/day divided in three doses daily (preferably every eight hours), taken orally at least 30 minutes pre or post meal until disease progression, death, or the patient discontinues treatment for adverse events, investigator's judgment, or other reasons. Patients who are able to proceed to allogeneic stem cell transplant will be able to resume crenolanib therapy post-transplant in an attempt to maintain remission.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Inclusion Criteria:

- Relapsed/refractory primary AML or AML secondary to antecedent hematologic disorder with an expected survival of 3 months or greater
- Patients must have tested positive for FLT3-ITD and /or other FLT3 activating mutations within < 60 days of the screening period.
- Age ≥18 years
- ECOG PS 0 – 2
- Adequate liver function, defined as total or direct bilirubin ≤1.5x ULN, ALT ≤3.0x ULN, AST ≤3.0x ULN. Exceptions for ALT and AST restrictions will be made in the setting of documented liver involvement with leukemia.
- 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 t1/2 (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 XVII for half-life information and drugs considered as FLT3 inhibitors for purposes of this trial..
- Negative pregnancy test for women of childbearing potential.
- Able and willing to provide written informed consent.
- Subjects who received crenolanib prior to and are within 30-90 days of an allogeneic stem cell transplant (HSCT) and have either no active GVHD where therapy has been initiated or GVHD where therapy has not been escalated within 14 days prior to start of study drug.

Exclusion Criteria:

- Absence of FLT3 activating mutation
- <5% blasts in blood or marrow at screening
- Concurrent chemotherapy, systemic immunosuppressants, 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 manifested as hepatitis surface antigen positive (HepBs Ag) or hepatitis C manifested as hepatitis C antibody positive
- For post HSCT, subjects who are within 29 days of an allogeneic transplant, and/or are on an unstable dose of immunosuppressive drugs for management or prophylaxis of GVHD or have escalated therapy for GVHD within 14 days of starting study drug and/or have >/=Grade 2 persistent non hematological toxicity related to the transplant or did not receive crenolanib prior to HSCT

- Evidence of lack of engraftment if post allogeneic transplant
- Unable to swallow pills
- Major surgical procedures within 14 days of Cycle 1 Day 1 administration of crenolanib.
- Unwillingness or inability to comply with protocol.

Test Product, Dosage and Mode of Administration:
Crenolanib besylate taken as follows:

1. For patients with active relapse and given as reinduction, 200mg/m^2/day divided in three doses daily (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. (Appendix III) Concurrent hydroxyurea (maximum 5g total daily dose) is permitted for the first 14 days of study therapy.
2. For patients continuing therapy as maintenance after allogeneic stem cell transplant (HSCT), the same dose of crenolanib most recently tolerated by the patient during induction will be restarted. Patients will complete a daily diary to record the date, time and amount (number of tablets) of crenolanib taken and eating schedule (Appendix III)

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. Subjects will take crenolanib besylate daily as reinduction and may resume as maintenance after allogeneic stem cell transplant, until their disease has progressed, the patient has died, or the patient discontinues for adverse events, investigator's judgment, or other reasons.

Subjects who have discontinued will continue to be followed 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. Descriptive statistics will be presented for all categories of each best response category. Duration of response and PFS will be listed and additionally summarized using Kaplan-Meier methodology. In addition, if at any time unacceptable toxicity is encountered in more than 33% of patients, the accrual will stop and lower doses may be investigated.

4. Abbreviations and Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that AROG is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
Case Report Form (CRF)	Sometimes referred to as clinical report form: a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
Consent	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. [Patients/Subjects] entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.
End of Study (trial)	The date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.

Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Interim Analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Institutional Review Board/Ethical Review/Board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial.
Patient	A study participant who has the disease or condition for which the investigational product is targeted.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, radiology and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
Treatment-Emergent Adverse Event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]).
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
CBC	complete blood count
CN-AML	cytogenetically normal acute myeloid leukemia
CT	computerized tomography

CR	complete response
CRF	case report form
CRi	complete remission with incomplete hematological recovery
CRp	complete remission with incomplete platelet recovery
DFS	disease-free survival
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
FDR	fixed dose rate
FLT3	FMS-like Tyrosine Kinase 3
GCP	good clinical practice
GGTP	gamma glutamyl transpeptidase
ICD	informed consent document
ICH	International Conference on Harmonization
IHC	immunohistochemistry
ITD	internal tandem duplication
LFTs	liver function tests
mm	millimeter
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03
NONMEM	nonlinear mixed effect modeling
ORR	overall response rate
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PET	positron emission tomography
PFS	progression free survival
PR	partial response
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SUV	standardized uptake value
TKD	Tyrosine Kinase Domain
TKI	Tyrosine Kinase Inhibitor
ULN	upper limit of normal

5. Background

5.1 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]

5.2 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 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 ITD or FLT3 mutant AML.

5.3 FMS-like Tyrosine Kinase 3 (FLT3)

FMS-like tyrosine kinase 3 (FLT3) is a receptor tyrosine kinase with important roles in hematopoietic stem/progenitor cell survival and proliferation and belongs to the class III receptor tyrosine kinase (RTK) family. The schematic of FLT3 is provided in Figure 5.1.[3] In normal human hematopoiesis, FLT3 expression is restricted to immature hematopoietic progenitors including $CD34^{+}$ hematopoietic stem cells (HSCs).[4]

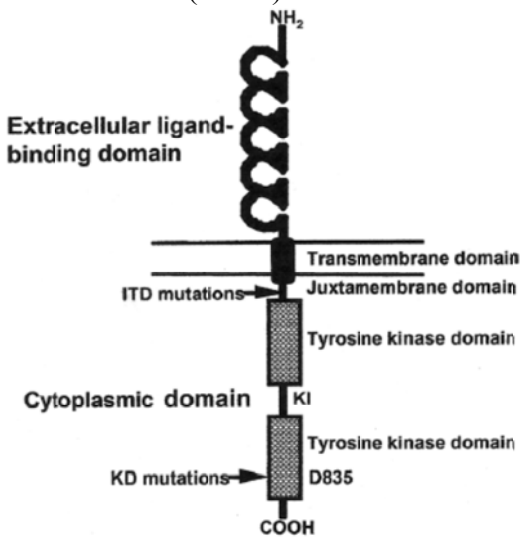

Figure 5.1. Schematic of FLT3 representing the domains: transmembrane, juxtamembrane and tyrosine kinase and the mutation locations of ITD and KD.[3]

5.4 FLT3 in AML

Mutations within the *FLT3* gene have been detected in up to 35% of AML patients and represent one of the most frequently identified genetic alterations in AML.[5] In addition, approximately 5%-10% of AML patients harbor point mutations within the second TKD. In most cases, these mutations result in a substitution of tyrosine for aspartic acid at codon 835. FLT3-TKD mutations cause constitutive activation of the FLT3 receptor, aberrant activation of downstream signaling pathways.

5.4.1 Downstream Pathways of Normal FLT3

Binding of its ligand, FLT3-ligand (FL) 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.[6] These actions affect the activation of further downstream PI3K/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways.[7] Bruserud et al. reported that exogenous FL increases blast proliferation for not only patients with wild-type FLT3 but also patients with FLT3-TKD mutations.[8] Therefore, FL-mediated triggering of FLT3 appears to be important for both wild-type and mutant FLT3 signaling.

Significant literature is available that implicates FLT3-D835 mutations as a key activating mechanism in a subset of AML and which thus could be targeted for therapy. [9-14] In addition, the FLT3–TKD mutations are associated with poor clinical outcome emphasizing the potential benefit in targeting cells with FLT3 targeted TKI.[15]

In 2008, Whitman et al. determind the prognostic relevance of FLT3 D835 mutations (FLT3-TKD) in cytogenetically normal acute myeloid leukemia (CN-AML).[16] They excluded patients with FLT3 internal tandem duplications and compared treatment outcome of 16 de novo CN-AML patients with FLT3-TKD with that of 123 patients with wild-type FLT3 (FLT3- WT), less than 60 years of age and similarly treated. Although all FLT3-TKD patients and 85% of FLT3-WT patients achieved a complete remission (P = 0.13). Disease-free survival (DFS) of FLT3-TKD patients was worse than DFS of FLT3-WT patients (P=0.01; estimated 3-year DFS rates, 31% vs 60%, respectively).

5.5 Crenolanib is a Potent Inhibitor of Type III Receptor Kinases and their Constitutively Active Mutations

Crenolanib besylate is an orally bioavailable benzimidazole, selective and potent inhibitor of type III receptor kinase FLT3 and its 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. [17] The CAS registry number is 670220-93-6.[18]

Crenolanib is a specific and potent inhibitor of class III receptor tyrosine kinases (RTKs) (Table 5.1). Crenolanib has sub-nanomolar K_d against the wild-type receptors FLT3 (0.74nM, Table 5.1.). 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.

Table 5.1. Activity of crenolanib against type-III receptor kinases[22]

RTK	Crenolanib K_d
FLT3	**0.74 nM**
PDGFRβ	2.1 nM
PDGFRα	3.2 nM
Kit	78 nM
CSF1R	30 nM

5.5.1 Crenolanib has High Binding Affinity against the FLT3 Mutant Isoforms D835H and D835Y

Crenolanib was evaluated in a K_dELECT assay (DiscoverRx, San Diego, CA) to determine its affinity against wild type FLT3 as well as its mutant isoforms. In these assays, crenolanib was found to have sub-nanomolar K_d for both FLT3-D835H and D835Y, which are found in about 7% of AML cases. These FLT3-TKD mutations, D835Y and D835H, are intrinsically resistant to almost all currently available FLT3-targeted TKIs. In clinical trials, patients progressing on sorafenib and quizartinib have been found to develop resistance through secondary D835H and D835Y mutations respectively.

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-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-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 5.2).[19]

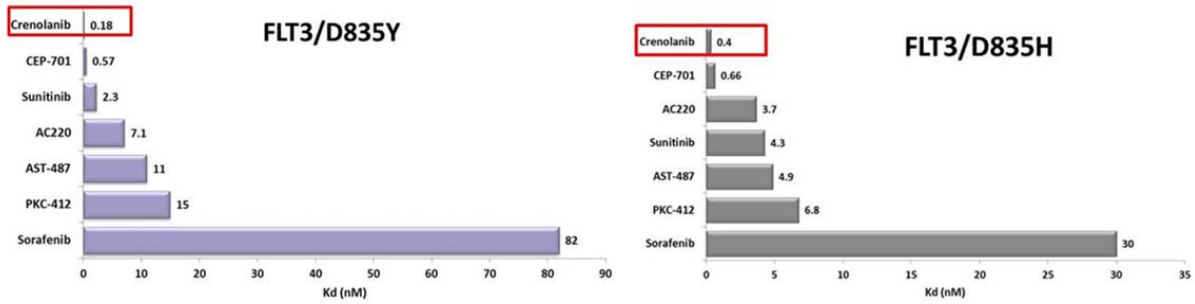

Figure 5.2. K_d measurements of crenolanib, sunitinib, CEP-701(lestaurtinib), AC-220 (quizartinib), sorafenib etc, with FLT3/D835Y and FLT3/D835H. Assay signals were normalized to facilitate comparison. [19, 22]

Activity of crenolanib against both wild-type as well as D835Y FLT3 kinase was evaluated in the Millipore IC_{50} profiler assay. This system allows for the direct measurement of phosphorylation with superior sensitivity using phosphocellulose (PH) filter plates. This assay system is a direct enzymatic measurement with "gold standard" radiometric filter binding format. In this assay, the IC_{50} of crenolanib against wild type FLT3 was 3nM and was even lower at 2nM against FLT3 with the D835Y mutation, confirming the activity of crenolanib against both the wild type and mutant FLT3 receptors

In contrast to sorafenib and quizartinib, which bind to the non-phosphorylated form of kinases (classified as type II TKI), crenolanib preferentially binds to the phosphorylated from of kinases (type I TKI).[19] Such constitutively phosphorylated FLT3 receptors are a consequence of D835 TKD mutations which makes resistant to both sorafenib and quizartinib but potentially sensitive to crenolanib. This high affinity of crenolanib to constitutively phosphorylated TKD mutants is not limited to just FLT3 but has also been seen in analogous activating mutants found in PDGFRA (D842V) as well c-kit (D816V).

5.5.2 Crenolanib is Active against Leukemic Cell Lines and Primary Blasts with FLT3-D835

Crenolanib not only inhibited phosphorylation of the wild type FLT3 receptor in SEMK2 cells, but also inhibited phosphorylation of the FLT3-D835Y TKD mutation in Ba/F3 cells transfected with vectors expressing FLT3-D835Y (Figure 5.3). The IC_{50} of crenolanib against the D835Y, TKD mutation of FLT3 was found to be 8.8nM.

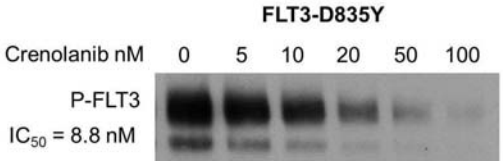

Figure 5.3. Activity of crenolanib against FLT3-D835Y mutation transfected in Ba/F3 cells (Unpublished, data on file).

In leukemic blasts from a newly diagnosed AML patient with the FLT3-D835V mutation, FLT3 phosphorylation was inhibited by crenolanib but was resistant to sorafenib and quizartinib (Figure 5.4).

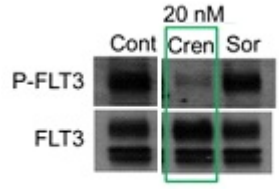

Figure 5.4. Leukemic blasts with the FLT3-D835V mutation were incubated with 20nM of crenolanib (Cren) or sorafenib (Sor) In contrast to sorafenib, crenolanib was able to provide near complete (>90%) inhibition of phosphorylated FLT3.[23]

5.5.3 Leukemic Blasts from Patients who Relapsed on FLT3 TKI Therapy Were Inhibited by Crenolanib

Leukemic blasts were obtained from a patient who had been treated with quizartinib and subsequently underwent an allogeneic transplantation. The patient's leukemic blasts had a FLT3/D835 mutation in the background of a FLT3/ITD mutation. Leukemic blasts obtained at the time of post-transplant relapse showed sensitivity to crenolanib in an MTT assay (IC_{50} of 26nM); with no sensitivity to sorafenib (Figure 5.5).

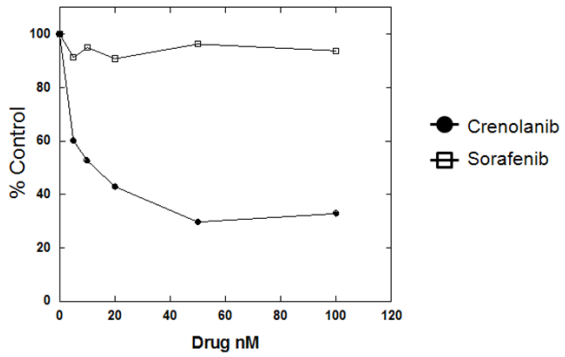

Figure 5.5. In primary patient blasts, crenolanib was the most potent inhibitor against FLT3/D835 in comparison to sorafenib.[23]

5.5.4 Phase I/II Clinical Studies of Oral Crenolanib Show that it is well absorbed and well tolerated

Crenolanib has been clinically evaluated as a single agent in a dose-finding and dose-ranging phase-I 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, one treatment related death has reported in 200 patients treated with crenolanib both as a single agent and in combination. This death occurred during phase Ib evaluation of crenolanib with docetaxel and axitinib in a patient with metastatic NSCLC and liver metastases who developed progressive liver failure and died. This death was classified as possibly related to study drug although progressive metastatic disease in the liver was not excluded.

The most frequent non-hematological grade 1/2 toxicities were diarrhea, nausea, and vomiting (Table 5.2). 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, and decreased lymphocyte count. 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 5.2. Incidence of treatment-related AEs occurring in ≥ 5% of the study population treated with single agent crenolanib, data as of May 2013

	NCI CTC Severity Grade				**Total patients = 125**	
Adverse Event	**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

QT prolongation has been observed in only two patients treated with single agent crenolanib

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 criteria, 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 Table 5.3. 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 Table 5.3.

There were two grade 1 QT interval prolongations observed in the 59 patients treated, that resolved without need for study drug interruption. No grade 2/3/4 QT interval prolongation have 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.

Table 5.3. Summary of QTc (Fridericia correction (A) and Bazett correction (B)) both baseline and worst on-study.

Summary of QTc (Fridericia correction) Baseline and Worst On-Study

Treatment Group: Over All

QTc interval(msec)	Baseline (N=59) n	(%)	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	

Summary of QTc (Bazett correction) Baseline and Worst On-Study

Treatment Group: Over All

QTc interval(msec)	Baseline (N=59) n	(%)	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)

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.

Effect of crenolanib on c-kit and potential for myelosuppression

Crenolanib has Kd for c-kit of 78nM as compared to FLT-3 of 0.74nM and could potentially not inhibit c-kit at doses that are adequate to inhibit FLT-3. 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 solely attributable to drug has been seen in the adult patients with AML treated to date with crenolanib. In addition, no greying of hair has been observed in any patients treated till-date.

Because of the poor reported results in treating relapsed FLT3 mutant AML with standard salvage approaches, especially those with D835 activating mutation, this trial will evaluate the safety of crenolanib as reinduction therapy for such patients and allow continuation of therapy after receipt of allogeneic stem cell transplantation (HSCT) to determine overall efficacy for this poor risk group of patients.

6. Patient Eligibility

6.1 Inclusion Criteria

- Relapsed/refractory primary AML or AML secondary to antecedent hematologic disorder with an expected survival of 3 months or greater
- Patients must have tested positive for FLT3-ITD and /or other FLT3 activating mutations within < 60 day screening period age ≥18 years
- ECOG PS 0 – 2 (Appendix II)
- Adequate liver function, defined as total or direct bilirubin ≤1.5x ULN, ALT ≤3.0x ULN, and AST ≤3.0x ULN. Exceptions for ALT and AST restrictions will be made in the setting of documented liver involvement with leukemia
- 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 antileukemic therapy (except hydroxyurea) prior to the first dose of crenolanib as follows: for 14 days for classical cytotoxic agents and for five times the t1/2 (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 XVII for half-life information and drugs considered as FLT3 inhibitors for purposes of this trial.
- Negative pregnancy test for women of childbearing potential
- Able and willing to provide written informed consent
- Subjects who received crenolanib prior to and are within 30 to 90 days of receipt of a allogeneic stem cell transplant (HSCT) and have either no active GVHD where therapy has been initiated or GVHD where therapy has not been escalated within 14 days prior to start of study drug.

6.2 Exclusion Criteria

- Absence of FLT3 activating mutation
- <5% blasts in blood or marrow at screening
- Concurrent chemotherapy, systemic immunosuppressants, 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 manifested as hepatitis B surface antigen (hepBs Atg) positivity or hepatitis C manifested as hepatitis C antibody positive.
- For post HSCT, subjects within 29 days of an allogeneic transplant, and/or are on an unstable dose of immunosuppressive drugs for management or prophylaxis of GVHD or have escalated therapy for GVHD within 14 days of starting study drug, and/or have >/=Grade 2 persistent non hematological toxicity related to the transplant or did not receive crenolanib prior to HSCT
- Evidence of lack of engraftment if post allogeneic transplant

- Unable to swallow pills
- Major surgical procedures within 14 days of Cycle 1 Day 1 administration of crenolanib.
- Unwillingness or inability to comply with protocol

6.3 Discontinuations

6.3.1 Discontinuations of Patients

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be immediately discontinued from the study drug unless specific approval is obtained from the IRB.

In addition, patients will be discontinued from the study drug but continued to be followed for survival data in the following circumstances:

- The patient experiences unacceptable toxicity as defined in Section 8.7 The patient is non-compliant (see Section 8.10).
- The investigator decides that the patient should be withdrawn, for example due to intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. AROG or its designee is to be alerted immediately (see Section 11.1).
- The patient or attending physician requests that the patient be withdrawn from the study.
- Enrollment in any other clinical trial involving an off-label use of an investigational drug or device or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The investigator or AROG stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

Patients in these circumstances will be followed as per the Study Schedule (appendix IV) and section 11.1.7.

For patients lost to follow-up or undergoing initiation of another drug therapy including allogeneic HSCT, the study schedule will be stopped but patients should be followed for survival data if at all possible.

6.3.2 Discontinuation of Study Sites

Study site participation may be discontinued if AROG, the investigator, or the ethical review board of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. Sites may also be discontinued if it is unable to accrue an adequate number of patients on the trial.

6.3.3 Discontinuation of the Study

The study will be discontinued if the site IRB judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice. The study could also be discontinued at any time at the sole discretion of the sponsor, AROG Pharmaceuticals, LLC.

7. Treatment Plan

7.1 Summary of Treatment

The study will enroll AML patients with FLT3 D835 and/or other FLT3 activating mutations. Patients in relapse will be treated with crenolanib at 200mg/m^2/day divided as three times a day (preferably every eight hours) continuously until they fulfill one of the criteria for study discontinuation (see Section 6.3) or proceed to allogeneic stem cell transplant.

Patients currently enrolled at 100mg TID (protocol v3.0) can be switched to the dosing based on BSA, see table 8.4, as per investigators discretion. If patients enrolled under v3.0 are continued on their current dose without BSA based dosing, continue study procedures from the current time point as outlined under Study Schedule (Appendix IV) of this version of the protocol (v4.0)

After allogeneic HSCT, patients who received crenolanib prior to transplant may resume crenolanib as maintenance on study post-transplant, if in remission at the same dose which was tolerated at the time of study drug hold prior to HSCT.

Patients who did not receive crenolanib preHSCT will not be able to receive crenolanib as maintenance therapy under this protocol.

Patients receiving less than 28 days of study dug as induction therapy will be replaced for efficacy evaluation. All patients will be assessed for toxicity

Study drug will be stopped if patients demonstrate evidence of relapsed disease as determined by the investigator.

7.2 Study Design

Fourteen relapsed/ refractory AML patients with FLT3 activating mutations will be treated with crenolanib daily as reinduction until they meet one of the criteria for discontinuation. After HSCT, patients who received crenolanib prior to transplant and achieved response may continue on study post-transplant with maintenance crenolanib. Until they meet one of the criteria for discontinuation. Subject efficacy evaluations will be performed at scheduled time points. These include: monthly bone marrow biopsy in the first two months, and then every three months for as long as criteria for CR/CRi is maintained. At loss of CR/CRi, bone-marrow biopsy will be performed only as clinically indicated to exclude toxicity issues such as pancytopenia due to study drug versus myelosuppression from progressive AML. Subjects' best clinical response will be recorded, as well as the response at 2 months. Subjects not in CR/Cri by the end of month 2 but showing clinical benefit will be allowed to continue therapy at the discretion of the physician.

7.3 Supportive Care Guidelines

Supportive measures including blood and platelet transfusions, antimicrobials, etc. are permitted. The administration of hematopoietic colony stimulating factors is not permitted.

Other chemotherapy, investigational cytotoxic agents, radiation, or biologic therapy is prohibited while the subject is on study with the following exceptions during cycle 1:

1. During the first 5 days of cycle 1 of study only, subjects may receive leukapheresis (not more than three procedures per week and not more than five procedures in total) to control elevated blast and/or platelet counts
2. hydroxyurea (up to a maximum of 5 gm /day) for a maximum of 14 days may be administered during cycle 1.
3. Leukapheresis and hydroxyurea may be administered together according to the guidelines above.

8. Study Procedures

After providing informed consent, if meeting the screening inclusion/exclusion criteria, and after having baseline evaluations performed within 28 days prior to first dose of study drug patients will be enrolled in the study.
The following assessments will be performed after completion of the informed consent and within 28 days of start of study drug except as otherwise specified:

8.1 Baseline Screening

1. Medical history (includes documentation of current medications and allergies)
2. Height, weight, vital signs
   ECOG Performance Status (Appendix II)
3. Pregnancy test for women of child bearing capacity
4. A complete history and physical, documentation of all disease, concomitant medications and performance status
5. CBC, platelet count, differential
6. Creatinine, total bilirubin, ALT, and AST
7. Bone marrow aspirate within 14 days preceding study drug initiation. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose, if done within 6-months of enrollment)
8. Evaluation of FLT3-D835, FLT3-ITD and other mutational status (if not done < 60 days preceding study drug initiation).
9. Baseline EKG assessment

8.2 Evaluation during Treatment and Post Allogeneic Transplant

1. Patient visits are weekly (± 2 days) for Cycle-1, bi-weekly (± 4 days) for Cycle-2, once every cycle (±14 days) from Cycle-3 to Cycle-6, once every two cycles (± 1 cycle) thereafter. The flexibility is applied to all instances unless specified.
2. 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.
3. EKG measurements to be obtained at 1 hour (± 30 mins) post first or second dose, in accordance to the visit. If new drugs with known effect on QTc are to be co-administered with crenolanib, EKGs including a baseline prior to start of the new agent and 2-3 days after starting patient on combination of drugs is recommended. Weekly EKG x3 is also recommended for follow up and as needed for assessment based on patient's clinical condition. EKG can then be resumed per study schedule.
4. CBC with platelet count, differential (differential may be omitted if WBC is <0.5 $x10^9$/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).
5. 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).

6. Bone marrow aspiration (with two additional aspirates) should be taken at these time points: cycle 2 day 1 (+4 days), then cycle 3 day 1 (+/- 4 days). Following which every 3 cycles (+/- 1 cycle) as long as criteria for CR are maintained. At loss of CR, bone-marrow biopsy would be performed only as clinically indicated to exclude toxicity issues like persistent pancytopenia due to study drug vs. from progressive AML. Aspiration sample for study purposes may also be submitted for patients not in CR if a marrow will be done for clinical purposes. Handling of bone marrow specimens is outlined in section 8.13, lab manual, and appendix XI.
7. Samples for translational research including pharmacokinetic analysis, whole-blood phospho-flow cytometry and plasma inhibitory assay will be obtained as defined in section 8.13.and lab manual. 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.
8. Procedures that are to be performed at the planned patient visits will be granted an exception only if the patients are hospitalized and unable to travel to the study sites. In that case, the investigator is responsible to ensure that the planned protocol procedures are performed at a local hospital. Source documents shall be obtained and information recorded onto study CRFs.

8.3 Treatment with Crenolanib (CP-868,596)

This study involves an assessment of crenolanib administered orally for the treatment of relapsed /refractory AML with FLT3 activating mutations. Responding patients who proceed to allogeneic stem cell transplant may be candidates to continue crenolanib as maintenance post-transplant.

All patients receiving study drug in relapse or with refractory disease will be administered 200mg/m^2/day divided as three times a day (preferably every eight hours) daily, 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 if it was taken either with or without food. (Appendix III). Tablets should be swallowed whole and not be crushed or dissolved.

Dosing will be three times daily, beginning on Day 1 through Day 28, for a 28 day cycle. The starting dose will be 200mg/m^2/day divided as three times a day (preferably every eight hours) (Table 8.1). The start of a cycle is denoted by the ingestion of study drug.

Table 8.1. Baseline Treatment Regimen

Regimen	**Dose**
All patients	Day 1 through Day 28 200mg/m^2/day divided as three times a day (preferably every eight hours)taken orally at least 30 minutes pre or post meal

Patients may receive multiple cycles of treatment as described in Section 8.7.5.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient/site personnel, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to AROG or its designee at the end of the study. Study medication that has been dispensed but remains unused at the end of the cycle is recorded by the site personnel and either safely discarded, if opened, or returned, if unopened.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be handled. If a patient vomits after drug ingestion, no replacement dose is to be taken; the patient can continue to take the remaining doses as planned. Missed doses will not be made up, and leftover drug should be returned to the study site upon patient follow up.

Counting Cycle Days: If drug is held or a dose is 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 as missed. If drug is held or missed for a day or more, the cycle should continue as if uninterrupted. Counting days of a cycle should be ongoing without disruption. 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.

Continuation of crenolanib after allogeneic transplantation as maintenance therapy:
Crenolanib will be held during the transplant period by stopping drug 72 hours prior to start of conditioning and resuming no sooner than 30 days post stem cell infusion.

For patients in CR/CRi after allogeneic transplant, crenolanib may be resumed at the same dose of crenolanib tolerated as induction when crenolanib was held. Patients will complete a daily diary to record the date, time and amount (number of tablets) of crenolanib taken and if it was taken either with or without food (Appendix III). Tablets should be swallowed whole and not be crushed or dissolved/

Patients may receive multiple cycles of treatment as described in Section 8.7.5. Follow up of patients on post-transplant crenolanib is outlined in section 8.2

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient/site personnel, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to AROG or its designee at the end of the study. Study medication that has been dispensed but remains unused at the end of the cycle is recorded by the site personnel and either safely discarded, if opened, or returned, if unopened.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be handled. If a patient vomits after drug ingestion, no additional tablets should be taken on that day. Missed doses will not be made up, and leftover drug should be returned to the study site upon patient follow up

Counting Cycle Days: If drug is held or a dose is 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 as missed. If drug is held or missed for a day or more, the cycle should continue as if uninterrupted. Counting days of a cycle should be ongoing without disruption. 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.

8.4 Materials and Supplies

Crenolanib besylate is supplied as 100mg and/or 20mg tablets for oral administration in 42 count bottles or 30-count bottles. Crenolanib besylate 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 requirements.

8.5 Method of Assignment to Treatment

All patients will receive crenolanib. Patients who meet all criteria for enrollment will be considered enrolled into the study at Day 1 of Cycle 1.

8.6 Rationale for Selection of the Baseline Dose for Current Protocol Version 4

Dose of 200mg/m^2/day divided as three times a day

In vitro experiments have demonstrated that crenolanib inhibits the phosphorylation of FLT3-D835 (FLT3-D835Y/H) and FLT3-ITD mutations with an IC50 of approximately 9nM and 2nM, respectively, in culture medium. In studies performed on plasma, the IC50 observed was 34nM against the FLT3-ITD mutation (23). FLT3 inhibition studies suggest that sustained inhibition of FLT3 phosphorylation approximately 10-15 fold above IC50 is required to achieve meaningful clinical benefit, taking into account FLT3 expression in both stromal and blast cells. We hypothesize that at least 680nM, or 20-fold the IC50, is needed for crenolanib to penetrate into bone marrow and maintain a sustained minimum concentration.

Crenolanib serum concentration-time data were modeled with a two-compartment structural model using a maximum likelihood estimation method as implemented in ADAPTII. Individual Bayesian post hoc parameter estimates were obtained for the volume of distribution of the central compartment (V_c), elimination rate constant (K_e), and the intercompartmental transfer rate constants (K_{cp} and K_{pc}). These parameter values were then extrapolated to a new population of 1,000 patients by pooling and random resampling. The concentration-time curves were then simulated out to steady-state (100 mg TID) using a differential equation solver for a two compartment model with first-order absorption and first-order elimination scripted in R. This Monte Carlo resampling scheme accounts for the variability in pharmacokinetic parameters and

allows for estimation of 95% confidence intervals of the concentration-time estimates indicated by the shaded regions on the plots below (figure 8.1).

The modeling/simulation cycle described above was performed with combined data from two adult studies (19 patients, ARO-BRE-001 (NCT01229644) and 002 (NCT01243346)) and one pediatric study ARO-003 (NCT01393912). This data was used to perform distribution of the BSA-normalized crenolanib pharmacokinetic parameters and the expected distribution of BSA in an adult population to perform 1,000 Monte Carlo simulations for each regimen. In figure 8.1, the shaded regions represent the 95% CIs for each simulation. The patients' dosing interval is considered to be every eight hours. Although the drug would be administered three times a day on a "TID" schedule, it is important to understand that the simulation was performed using an every eight hour dosing schedule and every attempt should be made to dose the drug on this schedule.

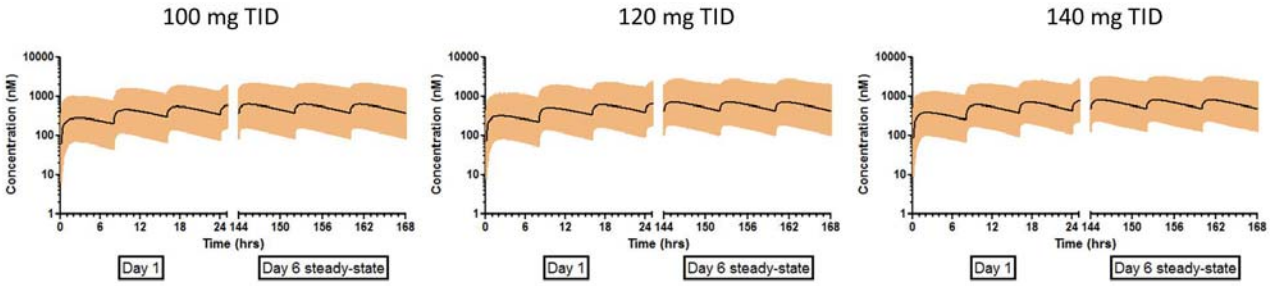

Figure 8.1. The PK simulation for TID (median +/- SD) plotted based on a simulation of data from 19 adult patients and pediatric patients.

The serum PK results of the 16 AML patients enrolled to date at 100mg TID across two clinical studies show that fifteen have cycle 1 day 15 average trough levels of 444nM (standard error ±15nM), below the theoretical target of 680nM required to inhibit FLT3 signaling in bone marrow. In addition, the Pk data suggest that crenolanib is slowly absorbed with a t-max of 2-4 hours and mean terminal half-life ranging from 8.6-9.5 hours. This suggests the currently administered crenolanib dose of 100mg TID (protocol v3) is insufficient to achieve adequate sustained inhibition of FLT3 kinase activity. As of May 2013, of the 16 patients enrolled across two clinical studies, 4 have achieved a CR (1CR/3CRi) with 6 others having some short lived reduction in blast cells in either blood or marrow and another 4 patients showing no response. In the 6 patients with blast decrease, blast reduction occurred by 21 days but was not sustained. These results suggest pharmacologic failure for most patients at this initially selected dose of 300mg/day (100mg/TID). In addition, AML patients over 85kg did not achieve sustained responses and are potentially underdosed on a flat-dose schedule.

In contrast to the flat mg/day dosing schedule currently given on this trial under protocol v3, an ongoing phase I trial (NCT01393912) in pediatric patients with malignant brainstem glioma has treated 49 patients at four escalating dose levels of single agent using mg/m2/day dosing. Nine patients have received crenolanib at 220mg/m2 QD as a single daily dose. Six out of these 9 patients were on study drug for the DLT period of 28 days. Two patients experienced DLT of transaminase elevations and stopped crenolanib therapy with subsequent resolution of abnormal

labs. Thus in the pediatric population 220mg/m2 given as one single daily dose approaches MTD but otherwise yields no other significant toxicities.

Because a single daily dose achieves higher peak concentrations of drug, we have hypothesized that once daily dosing is associated more commonly with potential toxicities such as LFT elevations; and a BID or TID schedule will lower peak drug concentrations potentially allowing more sustained dosing, less toxicity and improved pharmacokinetic profiles. At the current 100mg TID dose prescribed in this trial (protocol version 31) no substantial drug related toxicities have been observed. The most common drug related adverse events (AEs) reported as grade 1 or 2 nausea and vomiting. Two patients required dose reductions for Grade 3 and 4 transaminitis, which resolved once drug was held. Both were on two CYP3A4 inhibitors which may interfere with drug metabolism. Both patients tolerated 80 mg TID without transaminitis. A crenolanib dose of 200mg/m^2/day given as a TID schedule is postulated to result in a lower peak drug concentration and potential toxicities but provide adequate sustained dosing levels to reduce pharmacologic failure. Pharmacokinetic data will continue to be collected.

8.7 Dosing and Dose Modification of Crenolanib

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

All patients with relapsed/refractory AML will receive crenolanib induction therapy at a starting oral dose of 200mg/m^2/day divided three times a day (preferably every eight hours) continuously for 28 days for each cycle of treatment. Study drug should be taken at least 30 minutes prior to or following a meal..
Crenolanib will be held starting 72 hours prior to start of planned conditioning for HSCT. Study drug will be held for a minimum of 30 days post infusion of stem cells (day of HSCT).

Post HSCT crenolanib will resume at the dose level last tolerated prior to HSCT.

BSA will be capped at 2m^2 for large patients and 1.5m^2 for small patients. Therefore the highest starting study drug dose will be 400mg/day (2m^2 x 200mg/m^2/day) and lowest drug dose will be 240mg/day (1.5m^2 x 160mg/m^2/day-see dose reduction scheme table 8.4).

Because dosing increments based on BSA may not result in uniform doses given TID, the sponsor will provide detailed dosing instructions to the site. Upon enrollment, the site will provide the sponsor the patient's height, weight and BSA. Along with the acknowledgement of enrollment, the sponsor will provide the site with a dosing information sheet (Appendix XV) on which will be the calculated starting dose (dose level 0) with instructions for how much drug should be taken at each TID ingestion. Similar instructions will be provided on the dosing instruction sheet for dose level (+1), (-1) and (-2) should the patient require dose modification while participating on the study.

Patients currently enrolled under protocol version 3 can be continued at their current dose and dose escalated as defined in this protocol version 4 if without grade 3 or 4 toxicity and lack of response to study drug at the current dose.

Patients are strongly encouraged to be premedicated as for moderate to highly emetogenic therapy per ASCO 2011 guidelines. Patients will complete a daily diary to record the date, time and amount (number of tablets) of crenolanib taken, and if it was taken with or without food. (Appendix III)

Dose Escalation during induction and maintenance
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.

Table 8.2: Dose escalation guidance

Dose level	Crenolanib dosing
0	200 mg/m^2/day
+1	220 mg/m^2/day

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

Counting Cycle Days: If drug is held or a dose is 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 as missed. If drug is held or missed for a day or more, the cycle should continue as if uninterrupted. Counting days of a cycle should be ongoing without disruption. 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.

8.7.1 Dose Reductions for Crenolanib for Non-hematologic Toxicities During Reinduction and Post Allogeneic Transplant

Toxicities will be graded using the NCI CTCAE, Version 4.03 (Appendix VI).

For patients receiving crenolanib for reinduction therapy: Dose reductions for non-hematologic toxicities except nausea, vomiting, and diarrhea due to crenolanib will be done according to the schema in Table 8.3. Dose reductions are summarized in Table 8.4 and reductions below 160mg/m^2/day will lead to withdrawal from the study drug, in which case the patient will stop taking crenolanib, but will still be followed for outcomes as outlined in 8.12.

Table 8.3. Based on NCI CTCAE v4.03, Crenolanib Dose Reduction for Non Hematologic Toxicities Except Nausea, Vomiting, and Diarrhea related to study drug. Use toxicity grade at time of start of next planned cycle. Reassessment may be performed weekly to determine when to restart drug or dose modify. A 28-day deferment window is allowed to assess toxicities.

Toxicity (NCI Criteria)	Dose modification for patients taking crenolanib as reinduction
Grade 1 or 2	No dose modification
Clinically significant or persistent grade 2 despite optimal therapy	Hold drug until toxicity resolves to grade 1 or less. Restart drug at same dose level (Table 8.4).
Grade 3 or 4	Hold drug until toxicity resolves to grade 1 or less. Restart drug at next lower dose level (Table 8.4).

Table 8.4. Dose levels of Crenolanib During Reinduction

Dose Level	Crenolanib Daily Dose
Baseline	200mg/m^2/day
First dose reduction (-1)	180 mg/m^2/day
Second dose reduction (-2)	160 mg/m^2/day

For patients receiving maintenance crenolanib after allogeneic transplant: Start of maintenance crenolanib therapy is intended at the earliest time no sooner than 30 days but no longer than 90 days after allogeneic HSCT. Prerequisites for start of maintenance are a stable dose of immunosuppressive drugs for management or prophylaxis of GVHD or no escalation of therapy for GVHD within 14 days of starting study drug and/or have no more than Grade 2 persistent non hematological toxicity related to the transplant. Patients must have received crenolanib prior to HSCT to continue on to maintenance.

Maintenance therapy will start at the last dose tolerated during reinduction therapy. For example, if the patient was taking 180mg/m2/day prior to proceeding with HSCT, maintenance therapy will resume at 180mg/m2/day.

Dose reductions for non-hematologic toxicities except nausea, vomiting or diarrhea due to crenolanib will be done according to the schema in Table 8.5. For dose level reductions please refer to Table 8.6, and appendix XV. Dose reductions below 140 mg/m2/day are not planned and crenolanib will be stopped.

Table 8.5. Based on NCI CTCAE v4.03, Crenolanib Dose Reduction for Non-Hematologic Toxicities Post Allogeneic Transplant except Nausea, Vomiting, or Diarrhea related to study drug. Use toxicity grade at time of start of next planned cycle. Reassessment may be

performed weekly to determine when to restart drug or dose modify. A 28-day deferment window is allowed to assess toxicities.

Toxicity (NCI Criteria)	Dose modification for patients taking crenolanib post allogeneic transplant
Grade 1 or 2	No dose modification
Clinically significant or persistent grade 2 despite optimal therapy	Hold drug until toxicity resolves to baseline or grade 1 or less. Restart drug at same dose level (Table 8.6).
Grade 3 or 4	Hold drug until toxicity resolves to baseline or grade 1 or less. Restart drug at next lower dose level (Table 8.6).

Table 8.6. Dose adjustments of Crenolanib Post Allogeneic Transplant Maintenance therapy will start at the last dose level tolerated during reinduction therapy and dose adjustments made from that dose.

Current crenolanib dose:	Change crenolanib dose to:
100 mg PO TID*	80 mg PO TID
220 mg/m2/day	200 mg/m2/day
200 mg/m2/day	180 mg/m2/day
180 mg/m2/day	160 mg/m2/day
160 mg/m2/day	140 mg/m2/day

*for patients enrolled on v3 of this protocol, not on BSA-based dosing

8.7.2 Dose Reductions for Crenolanib for Hematologic Toxicities for Patients Taking Crenolanib as Reinduction and Post Allogeneic Transplant

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 two cycles 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 above.

  For patients taking crenolanib post allogeneic transplant, dose modification for hematologic toxicity will follow those outlined in Section 8.7.1 and tables 8.5 and 8.6

8.7.3 Dose Re-escalations for Crenolanib during induction and maintenance

In patients for whom the dose has been reduced due to toxicity, the dose may be re-escalated provided the patient has shown no clinical benefit and 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 to a max of 220 mg/m^2..

8.7.4 Cycle Delays

A cycle of therapy may be delayed for a maximum of 28 days to allow recovery from toxicities. If drug has been held for total duration of 56 days or more, patient will be discontinued from study.

8.7.5 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.

8.8 Blinding

This is an open-label study.

8.9 Concomitant Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on source documents as concomitant medication.

No other anticancer therapy including immunotherapy, hormonal cancer therapy, or experimental medications other than hydroxyurea (which is allowed during the first two weeks) will be permitted while patients are participating in this study. Radiation therapy will not be allowed. No hematopoietic growth factors will be permitted while patients are participating in this study. Any disease progression requiring other forms of specific antitumor therapy will be cause for discontinuation of study therapy.

At the discretion of the investigator, crenolanib can be administered with standard anti-emetic and anti-diarrheal premedication. Prophylaxis can be discontinued if patient tolerates crenolanib without significant nausea and vomiting.

Donor lymphocyte infusion (DLI) will be permitted after 2 cycles (56 days) of crenolanib therapy exclusive of any drug hold for resolution of toxicity.

8.10 Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

Definition of noncompliance: Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he or she takes <60% of the total amount of expected study drug taken in a visit interval.

In addition, to monitor patient compliance during the two first cycles, patients will be asked to complete a diary to record the date, time, and amount (the number of tablets) of crenolanib taken (Appendix III).

The following procedures will be employed to assure appropriate drug accountability:

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study drug packaging and unused material to the study site at each visit. The study site personnel will keep a record of all drug dispensed to and returned by the patients throughout the study. Study site personnel will return or destroy (as requested) all used, unused, and expired study drug for all patients.

8.11 Sample Collection and Testing

Appendix V lists the specific standard tests to be performed for this study.

8.11.1 Samples for Standard Laboratory Testing

Blood samples will be collected at the times specified in the Study Schedule (Appendix IV). Standard laboratory tests, including chemistry, liver function tests, and hematology panels, will be performed as outlined below.

- Cycle 1: labs twice weekly (at least 24 hours apart) for the first two weeks of cycle 1, then weekly (±3 days) for the second two weeks of cycle 1
- Cycle 2: labs every 14 days ±4 days
- Cycle 3 to Cycle 6: labs every 28 days ±14 days
- Cycle 6 onwards: once every two cycles (± 1 cycle)

A pregnancy test should be performed at study entry and at any time during the study if clinically indicated by history or clinical exam. Other clinical laboratory tests will be analyzed by either a central or a local laboratory. Appendix V lists the specific tests that will be performed for this study.

Investigators must document their review of each laboratory safety report

8.12 Follow up Visits

The Study Schedule in Appendix IV lists the specific follow up visits for this study.
The Study Schedule applies to patients receiving study drug. The calendar should re-commence as start of cycle 1 when drug is resumed post allogeneic transplant. Patients who have discontinued study drug for any reason should be followed for survival.

8.13 Translational Research

Translational studies to be evaluated include but are not limited to:

1. Pharmacokinetic analysis (Pk)
2. Whole-blood phospho-flow cytometry to detect activation of FLT3 and other signal transduction molecules in leukemic blasts from patients
3. Plasma inhibitory assay to assess if therapeutically adequate concentrations of crenolanib were achieved in each patient (PIA)
4. Bone marrow aspirate samples

Bone marrow samples will be collected at the time of marrow sampling with 2 additional aspirations drawn and placed in heparinized tubes. These samples will be refrigerated and shipped at 4-8^{o}C within 24 hours of collection to the laboratory specified in Appendix XII.

The participating institution will receive a laboratory kit containing blood collection tubes, labels, collection instructions from AROG for the collection of samples from consenting patients. Site should contact AROG (Appendix XIV)at to request a lab kit for each patient enrolled on the study.

Serum and blood for translational research will be obtained at multiple time points on Cycle 1, Day 1, a single trough level on Cycle 1 Day 2, at multiple time points on Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 3 Day 1. Additional serum and blood samples for translational research may be drawn at the discretion of the investigator.

Sampling Strategy

On Day 1 of Cycle 1, serial blood samples for PK, whole blood phosphoflow, and PIA will be drawn for translational research at the following time points: pre dose and at 30 (± 10), 60 (± 15), 120 (± 15) minutes, 4 (±1) hours, and 8 (±2) hours after crenolanib administration (Appendix VIII forms).

On Day 2 of Cycle 1 (24 (±6) hours), blood samples for Pk and PIA only will be drawn at a single time-point: **pre** first dose to obtain the trough levels of crenolanib. (Appendix VIII).

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.

On Day 15 of cycle 1, samples for Pk, whole blood phosphoflow, and PIA will be drawn at the following time points: pre dose prior to ANY study drug ingestion for the day, then 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 time point is obtained on day 15. (Appendix IX forms).**

On Day 1 of Cycle 2, and Day 1 of Cycle 3, samples for PK, whole blood phosphoflow, and PIA will be drawn at the following time points: pre dose prior to ANY study drug ingestion for the day, and 4 (±1) hours after administration of first crenolanib dose. **Do not administer subsequent doses of crenolanib until after 4 hour time point is obtained. (Appendix X forms).**

For dose escalations, repeat the Day 1 of Cycle 1 and Day 15 of Cycle 1 instructions.
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 X forms).
Optional bone marrow biopsy samples and concurrent whole blood samples may be collected at any time while the patient is on treatment, at the discretion of the investigator (Appendix X).

Sample Processing Instructions
See lab manual. *Other Correlative Studies*

Tissue cells 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. But the total blood drawn for these studies will be less than 400ml in any month.

9. Response Definitions

9.1 Response Criteria

Response criteria will be adapted from the International Working Group for AML.[21] Responders are relapsed/refractory patients receiving study drug as reinduction therapy who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

1. *Complete remission (CR):*
    a. Peripheral blood counts:
        i. No circulating blasts
        ii. Neutrophil count ≥1.0 x10^9/L
        iii. Platelet count ≥100 x10^9/L
    b. Bone marrow aspirate and biopsy:
        i. ≤5% blasts
        ii. No Auer rods
        iii. No extramedullary leukemia

2. *Complete remission with incomplete blood count recovery (CRi):*
    a. Peripheral blood counts:
        i. No circulating blasts
        ii. Neutrophil count <1.0 x10^9/L, or
        iii. Platelet count <100 x10^9/L
    b. Bone marrow aspirate and biopsy:
        i. ≤ 5% blasts
        ii. No Auer rods
        iii. No extramedullary leukemia

3. *Partial remission:*
    a. All CR criteria if abnormal before treatment except:
    b. ≥50 % reduction in bone marrow blast but still >5% or
    c. Marrow blasts <5% with persistent Auer rods

4. *Morphologic leukemia-free state:*
    a. Bone marrow: ≤5% myeloblasts

5. *Hematologic Improvement (HI):*
    Hematologic response must be described by the number of positively affected cell lines.
    a. Erythroid response (E) (pretreatment Hgb <11 g/dL)
        i. Hgb increase by ≥1.5 g/dL
    b. Platelet response (P) (pretreatment platelets <100 x10^9/L)
        i. Absolute increase of ≥30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
        ii. Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
    c. Neutrophil response (N) (pretreatment ANC <1.0 x10^9/L)
        i. At least 100% increase and an absolute increase > 0.5 x 10^9/L

10. Statistical Considerations

10.1 Determination of Sample Size

The FLT3-3 D835 AML activating mutations have been refractory to currently available TKIs. An upper one-sided 75% confidence bound on the fraction of such patients who might respond to no treatment or ineffective therapy is 10%.
Therefore we will treat 15% response rate as our null hypothesis and submit 14 patients to this phase II trial. If at least 2 patients respond to treatment, the null hypothesis will be rejected. If the true response rate is 30%, this design will have 85.07% power and 8.61% type I error.

10.2 Toxicity Evaluation

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

10.3 Statistical and Analytical Plans

The primary end-point is overall response rate. We will use tests of the binomial proportion for both response and toxicity (Section 11). Descriptive statistics will be used for progression free survival and exploratory endpoints. Duration of response and PFS will be listed and additionally summarized using Kaplan-Meier methodology.

10.3.1 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.

10.3.2 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

10.3.3 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.

10.3.4 Concomitant Therapy

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

10.3.5 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

10.3.6 Primary Outcome and Methodology

Response criteria will be adapted from the International Working Group for AML, as stated in section 9.1.

10.3.7 Efficacy Analysis

The primary end-point is overall response rate (detailed in section 9.1). Descriptive statistics will be presented for all categories of each best response category. Duration of response and PFS will be listed and additionally summarized using Kaplan-Meier methodology. In addition, if at any time unacceptable toxicity is encountered in more than 33% of patients the accrual will stop and lower doses may be investigated.

10.3.9 Safety Analyses

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

- Adverse events,
- TEAEs,
- SAEs,
- Deaths,
- Discontinuations due to adverse events,
- Extent of exposure to study drug treatment,
- Hospitalizations,
- Use of key concomitant medications (for example, antipruritus medication).

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

10.3.10 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 postlock data will eventually be combined with the locked database and stored in a data library separate from the locked database.

11. Safety Evaluations and Appropriateness of Measurements

11.1 Safety Evaluations

11.1.1 Adverse Event Definition

An adverse event is defined as any condition which appears or worsens after participation in the study. All adverse events will be captured on the Adverse Event Case Report Form, whether or not it is felt to be related to the trial activities.

11.1.2 Serious Adverse Event Definition

ICH Guideline E6 defines serious adverse events as those events which meets any of the following criteria (Appendix VII):

- Fatal
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Hospitalizations that do not meet these criteria are:

- surgery or procedure planned prior to entry into the trial
- social reason in the absence of an adverse event

Study-specific clinical outcomes of death from PD should be reported as an SAE only if the investigator deems them related to use of the study drug.

11.1.3 Unexpected Adverse Events Definition

Any event occurring in one or more subjects participating in this research protocol in which the nature, severity, or frequency is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described (a) in the protocol-related documents, such as this protocol and the informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

11.1.4 Attribution

For reporting purposes, attribution is the assessment of the likelihood that an adverse event is caused by the research agent or protocol intervention. The attribution is assigned by the principal investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using one of the following three categories:

- Likely Related
- Possibly Related
- Not Related

Likely related means that the adverse event was most certainly caused by the procedures involved in the research.

Possibly related means that there is reasonable possibility that the adverse events may have been caused by the procedures involved in the research.

Not related means that the adverse event was due to an underlying disease, disorder, or condition of the subject, or may have been caused by other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

11.1.5 Adverse Event Reporting

AROG has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. During the study, site personnel will record any change in the condition(s) and the occurrence and nature of any adverse events.
After the Informed Consent Document (ICD) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to AROG or designee.

All AEs occurring after the patient receives the first dose of study drug must be reported to AROG or its designee via CRF. Investigators will be instructed to report to AROG or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, and/or drug delivery system via CRF.

Study site personnel will record any daily dosage that exceeds the maximum dosage in the protocol or in the relevant reference safety document (for example, clinical dosage section for humans in the Investigator Brochure), whichever is greater, via CRF.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to AROG or its designee via CRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Events leading to the clinical outcome of death due to disease progression will be included as part of the safety and efficacy analyses for this study and will not be reported to AROG or its designee as AEs via CRF, unless the investigator believes the event may have been caused by the study drug. In this case the death should be reported to the sponsor as a Serious Adverse Event and appropriate guidelines followed for SAE reporting.

Any clinically significant findings from labs, vital sign measurements, other procedures, etc. that result in a diagnosis should be reported to AROG or its designee.

11.1.6 Serious Adverse Event Reporting

Table 11.1 outlines adverse event and serious adverse event (SAE) assessment and follow–up guidelines.

Table 11.1. Adverse Events/Serious Adverse Events Assessment Guide

Time	After ICD/Before Drug	During Therapy	30-day Post-discontinuation follow-up period	Long-term follow-up period
Events to collect	AE/SAEs	New/ongoing AE/SAEs		New/ongoing SAEs
	Related to procedures	Regardless of relatedness to study treatment or procedures		Related to study treatment or procedures

Serious adverse event collection begins after the patient has signed informed consent and has received a tablet or more of study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert AROG or its designee of any serious adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. All cases are recorded on the CRF and copy of an SAE report is provided to AROG by the site.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events 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.

Study-specific clinical outcomes of death from PD should be reported as an SAE only if the investigator deems them related to use of the study drug.

Any event deemed serious within the 30-day post discontinuation follow-up period, regardless of relatedness to study drug or protocol procedure, must be reported immediately to AROG or its designee.

AROG or its designee will be alerted to SAEs occurring after a patient's 30-day post discontinuation follow-up only if the investigator believes that the event may have been caused by the study drug.

SAEs occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

All serious adverse events (SAE) will be reported to the study coordinator within 24 hours of the investigational staff's knowledge. This includes any event that occurs during the participation of the trial regardless of associated participation, severity or relationship.

11.1.7 Follow-up

All adverse events will be followed up according to Good Clinical Practice.
During Treatment: During study, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. A CTCAE rating will be assigned before each visit for any adverse events experienced during the previous visit period.

30-Day Post-discontinuation Period: Each patient will have a 30-day post-discontinuation follow-up evaluation after 30 days ± 5 days following the discontinuation of study treatment. Patients should be closely followed for AEs in order to detect delayed toxicity. A toxicity questionnaire will be completed by the patient, the patient's physician, or the patient's family member at the follow-up evaluation.

Long-Term Follow-Up Period (after the 30-day post-discontinuation period): Only new and ongoing serious adverse events (SAEs) thought to be related to study treatment or protocol procedures should be documented on the CRF and immediately reported to AROG or its designee via the designated transmission method. If drug-related toxicity is present beyond 30 days post-discontinuation, patients must be followed every 30 days until the toxicity resolves.

In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit-sleeping longer") to AROG or its designee via CRF.

Serious Adverse Event Follow Up
Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure

Study site personnel must alert AROG or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any adverse event from this study that results in one of the following outcomes (Appendix VII):

- Death (see exception noted below)
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events 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. Study-specific clinical outcomes of death from PD should be reported as an SAE only if the investigator deems them related to use of the study drug.

SAEs occurring after a patient has taken the last dose of study drug will be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure.

Any event deemed serious within the 30-day follow-up period, regardless of relatedness to study drug or protocol procedure, must be reported immediately to AROG or its designee.

AROG or its designee will be alerted to SAEs occurring after a patient's 30-day post discontinuation follow-up only if the investigator believes that the event may have been caused by the study drug.

11.1.8 Other Safety Measures

The schedule for laboratory testing is noted in Appendix IV, and the required tests are listed in Appendix V. While there are a number of blood tests, blood work being done is considered part

of routine care for patients undergoing therapy for relapsed AML. Some blood work may be viewed as being done more often than might be required in usual care but this is to ensure equal probability of ascertaining side effects in all patients.

11.2 Appropriateness of Measurements

All efficacy and safety assessments used in this study are appropriate for an oncology study (US FDA Guidance, May 2007). Overall response rate response is an appropriate primary endpoint for measuring initial activity of crenolanib in the targeted patient population (Crowley and Ankerst, 2006). Duration of response is an important endpoint to judge the quality of the response. In addition, progression free survival is an accepted endpoint in AML.

The Common Terminology Criteria for Adverse Events (CTCAE, version 4.03; NCI 2010) is an acknowledged scale used to evaluate adverse events in oncology trials.

12. Data Quality Assurance

To ensure accurate, complete, and reliable data, AROG or its representatives will do the following:

- Provide instructional material to the study site, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

In addition, AROG or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by AROG or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

12.1 Data Capture System

A paper data capture system will be used in this trial. Case report form (CRF) data will be encoded and stored in a clinical trial database. Any data that will serve as the source document will be identified and documented in the site's study file. Any data for which the CRF, or other paper documentation provided by the subject, will serve as the source document will be identified and documented in the study file.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1 Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The informed consent document (ICD) will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

13.2 Ethical Review

AROG must agree with all ICDs before they are submitted to the ethical review board (ERB) and are used at investigative site(s). All informed consent documents must be compliant with the International Conference on Harmonization (ICH) guideline on good clinical practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by AROG.

Documentation of ERB approval of the protocol and the ICD must be provided to AROG. The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

As well as required documentation required by the study site's ERB(s), the following will be provided:

- Current Study Protocol
- The current Investigator's Brochure or package labeling and updates during the course of the study
- Informed consent document

13.3 Regulatory Considerations

13.3.1 Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2 Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to an AROG representative.

13.3.3 Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most analyzable patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by AROG to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer will sign the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Appendix I. 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.

I. Study Information

Protocol Title:	A Phase II Study of Crenolanib Besylate in Subjects with Relapsed or Refractory Acute Myeloid Leukemia with FLT3-D835 Activating Mutations
Protocol Number:	ARO-004

II. Subject Information

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria-all must be YES (From IRB approved protocol)	**Yes**	**No**	**N/A**	**Supporting Documentation***
1. Relapsed primary or AML secondary to antecedent hematological disorder with an expected survival of 3 months or greater	☐	☐		
2. Presence of FLT3 activating mutation as tested within 60 days of enrollment.	☐	☐		
3. Age ≥18 years	☐	☐		
4. ECOG Performance Status 0 - 2	☐	☐		
5. Liver function: Transaminases ≤ 3x ULN Bilirubin ≤ 1.5x ULN	☐	☐		
6. Renal function: Total creatinine ≤ 1.5x ULN	☐	☐		
7. Recovery from toxicities of prior therapy (including HSCT) to no more than grade 1 (except alopecia)	☐	☐		

8. In the absence of rapidly progressing leukemia, subjects should have received no antileukemic therapy (except hydroxyurea) for 14 days (for classical cytotoxic agents) and for five times the half life of FLT3 inhibitors and antineoplastic agents that are neither cytotoxic nor FLT 3 inhibitors prior to the first dose of crenolanib.	☐	☐		
9. Negative pregnancy test for women of childbearing potential	☐	☐	☐	
10. Able and willing to provide written informed consent	☐	☐		
11. Subjects who received crenolanib prior to and are within 30-90 days of receipt of a HSCT and have either no active GVHD where therapy has been initiated or GVHD where therapy has not been escalated within 14 days prior to start of study drug.	☐	☐	☐	
Exclusion Criteria-All must be NO (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 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. Inability to swallow pills.	☐	☐		
6. HIV infection or active hepatitis B or C	☐	☐		

7. Subjects who have had HSCT and are within 29 days of an allogeneic transplant, and/or have clinically significant graft-versus-host disease requiring systemic treatment or did not take crenolanib prior to HSCT.	☐	☐	☐	
8. Unwillingness or inability to comply with protocol	☐	☐		
9. Major surgical procedure within 14 days of Cycle 1 of crenolanib				
10. Evidence of lack of engraftment if post HSCT				

*****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 II. 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 III. Patient Diaries: Crenolanib

Cycle No: _____

This section to be completed by Site Study Staff ONLY

SUBJECT ID | | | | | | | | |

SUBJECT INITIALS | | | |

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

Protocol ID: ARO - 004

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 - 004

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 - 004

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 - 004

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

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

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

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

Appendix IV. Study 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	(-)28	1	2	8	15	22	1	15	1	1		
Baseline Procedure												
Informed Consent	X											
Inclusion/Exclusion	X											
Demography, Relevant medical history, current medical conditions including AML-specific history	X											
Evaluation of FLT3-D835, FLT3-ITD, and other mutational status	X											
Routine Examination												
Prior/Concomitant medications, significant non-drug therapies	X	X					X		X	X	X	X
Physical examination[a]	X	X					X			X	X	X
EKG[b]	X	X										
Vitals, ECOG Performance Status, Weight	X	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[c]	X	XX		XX	X	X	X	X	X	X	X	X
Serum Chemistries[d]	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[e]		X	X		X		X		X			
Peripheral blood for correlative		X	X		X		X		X			

analysis[f]												
Disease assessment												
Bone marrow aspirations (x2)[g]	X	X					X		X	X		

[a] Physical exam can be done within ±4 days of start of cycle 1 and cycle 2 then every 2 cycles
[b] EKG measurements to be obtained at 1 hour (± 30 mins) post first or second dose, in accordance to the visit. If new drugs with known effect on QTc are to be co-administered with crenolanib, EKGs including a baseline prior to start of the new agent and 2-3 days after starting patient on combination of drugs is recommended. Weekly EKG x3 is also recommended for follow up and as needed for assessment based on patient's clinical condition. EKG can then be resumed per study schedule

[c,d] CBC includes platelet count, differential (differential may be omitted if WBC is $<0.5 \times 10^9$/L) and Chemistry panel including creatinie, 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 or designee 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.

[e,f] 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, and Day 1 of Cycle 2 and Cycle 3. Additional samples may be drawn at the discretion of the investigator.
[g] Two bone marrow aspirations will be collected on day 1 (+4 days) of the second cycle, day 1 (±4 days) of the third cycle, then every 3 cycles (+/- 1 cycle) for as long as CR is maintained. At loss of CR, bone-marrow biopsy will be performed only as clinically indicated to exclude toxicity issues.

Appendix V. 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	
Eosinophils	Alanine aminotransaminase (ALT/SGPT)
Basophils	Aspartate aminotransferase (AST/SGOT)
Platelets	
	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 Can be 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 VI. 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 VII. 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 VIII-A. ARO-004 C1D1 Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA:
Total daily 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 VIII-B. ARO-004 C1D1 Plasma Inhibitory Assay Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA:
Total daily 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 plasma inhibitory assay 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 VIII-C. ARO-004 C1D1 Whole Blood Phospho-Flow Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA:
Total Daily 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.*** List the scheduled and actual times of the collected 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			

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

Appendix IX-A. ARO-004 C1D15 Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total daily 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 (pre PK sample)			
30 (±10) minutes after dose (PK sample)			
4 (± 1) hours after dose (PK sample)			

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

Appendix IX-B. ARO-004 C1D15 Plasma Inhibitory Assay (PIA) Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total daily 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 collected 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 (pre PIA sample)			
30 (±10) minutes after dose (PIA sample)			
46 (± 1) hours after dose (PIA sample)			

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

Appendix IX-C. ARO-004 C1D15 Whole Blood Phospho-Flow Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total Daily 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 collected 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-A. ARO-004 C_D_ Pharmacokinetics Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total daily 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 (pre PK sample)			
4 (± 1) hours after dose (PK sample)			

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

Appendix X-B. ARO-004 C_D_ Plasma Inhibitory Assay Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total daily 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 collected samples in the chart below. List exact date and time of crenolanib administration. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible. ***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 X-C. ARO-004 C_D_ Whole Blood Phospho-Flow Data Collection Form

Study Accession #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA
Total Daily 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 collected samples in the chart below. List exact date and time of crenolanib administration. Scheduled time refers to the time that blood should be collected, and actual time refers to the actual time the blood was collected whether it is the same or different than the scheduled time. Blood should be collected as close to the scheduled time as possible. ***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. C_D_ Bone Marrow Aspiration: Data Collection Form

Study Acc #:	Study ID:	
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	BSA:
Total daily 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 sample volume or estimated mass, and note any collection issues in the chart below. Use an additional sheet if necessary.
Date of Dose: _____
Dose Administration Time: _____
Describe Dose Tolerance: _____

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

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

Appendix XII. 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. Whole-blood Phosho-flow Cytometry
Alexander Perl, MD
Abramson Cancer Center
Perelman Center for Advanced Medicine, West Pavilion, 2nd Floor
3400 Civic Center Boulevard
Philadelphia, PA 19104
(215) 573-8478
Alexander.Perl@uphs.upenn.edu

C. 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

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

Appendix XIII. 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 XIV. 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
E:pkambuj@arogpharma.com
M: 214.593.0512

Contact Information for notification of shipment of correlative studies samples

John Huang or Justin Rains
AROG Pharmaceuticals, LLC
E: lab@arogpharma.com
O: +1 214.593.0500
M: +1 817.849.0175
F: +1 214.594.0002

Appendix XV. Dosing Instructions for Relapsed/Refractory AML Patients

To be filled out by SITE:

Study ID: **ARO-004**	Today's Date:	Time form faxed from site:
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
BSA Calculation Method:	BSA:	Date/Time Confirmation received from site:

To be filled out by SPONSOR: See protocol section 8 for instructions on dose modification and application of appropriate dose levels.

Starting Dose Crenolanib (CP-868,596) Dose level 0 (mg/m^2): 200 mg/m^2/day	Calculated Crenolanib (CP-868,596) Total daily Dosage (mg) and instructions for divided dosing
First dose reduction: 180 mg/m^2/day	
Second dose reduction: 160 mg/m^2/day	
Dose escalation: 220 mg/m^2/day	
Time form faxed from Arog:	Confirmation received from site:

Appendix XVI. Dosing Instructions for Patients post HSCT

To be filled out by SITE:

Study ID: **ARO-004**	Today's Date:	Time form faxed from site:
Race:	Sex:	Date of Birth:
Height (cm):	Weight (kg):	
BSA Calculation Method:	BSA:	Date/Time Confirmation received from site:

To be filled out by SPONSOR: See protocol section 8 for instructions on dose modification and application of appropriate dose levels.

Starting Dose Crenolanib (CP-868,596) Dose level 0 (mg/m^2):	Calculated Crenolanib (CP-868,596) Total daily Dosage (mg) and instructions for divided dosing:
First dose reduction:	
Second dose reduction:	
Dose escalation:	
Time form faxed from Arog:	Confirmation received from site:

Appendix XVII. 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
KW-2449*	KW-2449	6.6 hours	33 hours	2
Lestaurtinib	CEP-701	9.2 hours	46 hours	2
R406*	R406	15 hours	75 hours	3
PLX3397*	PLX3397	20 hours	100 hours	4
Dovitinib	TKI258	24 hours	120 hours	5
Sorafenib	BAY-43-9006	27 hours	135 hours	6
Tandutinib	MLN518	33 hours	165 hours	7
Quizartinib	AC220	67.2 hours	336 hours	14
Sunitinib	SU11248	86 hours	430 hours	18
Midostaurin	PKC412	96 hours	480 hours	20

**No trade name is currently available*