CLINICAL STUDY PROTOCOL

PHASE 1/2 DOSE-ESCALATION, SAFETY, CLINICAL ACTIVITY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF THE ERK1/2 INHIBITOR BVD-523 IN PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA OR MYELODYSPLASTIC SYNDROMES

BVD-523-02

Drug Development Phase:	Phase 1/2
Investigational Product:	BVD-523
Indication:	Acute Myelogenous Leukemia or Myelodysplastic Syndrome
Sponsor:	BioMed Valley Discoveries, Inc. 4520 Main St. 16th Floor Kansas City, MO 64111
Protocol Version and Date:	Version 2, 18 November 2015

Conduct: Conducted in compliance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and in accordance with local regulatory requirements.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: BIOMED VALLEY DISCOVERIES, INC

I have read and understand the contents of Version 2 of this clinical protocol for Study No. BVD-523-02 dated 18 November 2015 and I agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this Study.

Approved By:

Nov. 24, 2015

Brent L. Kreider, PhD.
Chief Operations Officer, BioMed Valley Discoveries, Inc.

Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of Version 2 of this clinical protocol for Study No. BVD-523-02 dated 18 November 2015 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices and applicable FDA regulatory requirements:

Principal Investigator:

Name:

Title:

Institution:

Address:

Address:

Phone:

Fax:

Signature **Date**

PROTOCOL SYNOPSIS

Sponsor: **BioMed Valley Discoveries, Inc.**	**Investigational Product:** **BVD-523**	**Developmental Phase:** **Phase 1/2**

Title of Study:
Phase 1/2 Dose-Escalation, Safety, Clinical Activity, Pharmacokinetic and Pharmacodynamic Study of the ERK1/2 Inhibitor BVD-523 in Patients with Acute Myelogenous Leukemia or Myelodysplastic Syndromes

Protocol Number:
BVD-523-02

Indication:
Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS)

Objectives:

Primary objectives:

- To define the safety and tolerability of BVD-523 in patients with AML or MDS by determining the dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).
- To determine the pharmacokinetic profile of BVD-523 and selected metabolites in patients with AML or MDS.

Secondary objectives:

- To assess clinical response in patients with AML or MDS treated with BVD-523 at the recommended Phase 2 Dose (RP2D).
- To determine the progression-free survival (PFS) and duration of response (DOR) of AML or MDS patients treated with BVD-523 achieving CR (complete remission)/CRp (complete remission with incomplete platelet recovery).

Exploratory objective:

- To evaluate pharmacodynamic marker (biomarker) measures.

Methodology/Study Design:
BVD-523-02 is an open-label, multicenter, Phase 1/2 study with a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2).

Part 1 – Dose-escalation Phase: A classic "3+3" design will be used to establish dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). Three to six patients per treatment cohort will be assigned to receive sequentially higher oral doses of BVD-523 on a twice daily schedule (b.i.d.) for 21 days (a "Cycle"), starting at a dose of 300 mg. Patients will receive twice-daily oral doses of BVD-523 until disease progression, unacceptable toxicity, or a clinical observation satisfying another withdrawal criterion is noted. Treatment cycles will occur consecutively without interruption, except when necessary to manage adverse events. All dose-escalation decisions will be based on Cycle 1 safety data and doses will not be escalated unless the patients receiving the highest current dose have been observed for at least 21 days (1 cycle).

The 3 + 3 design will be conducted as follows. Initially, 3 patients will be enrolled to a cohort; the occurrence of a single drug-related DLT in one of these 3 patients will prompt enrollment of up to 3 additional patients to that same cohort. When more than 1 DLT occurs in ≤ 6 patients in a dosing cohort, dose escalation will be stopped and this dose level will be identified as the non-tolerated dose. Doses between the non-tolerated dose and the preceding lower dose, where ≤ 1 DLT occurred, may be explored to more precisely define the MTD. This strategy allows for a rigorous determination of MTD, especially if the dose increase that resulted in determination of the non-tolerated dose is relatively large (i.e., > 50%).

During the study, the Sponsor and Investigators may request that cohorts be enlarged or that evaluation of intermediate doses between 2 planned escalation steps be explored. Such requests will be discussed with the Investigator(s), Sponsor and Medical Monitor, and should be based on all data existing at that time, including

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safety and clinical activity, determinations of pharmacokinetics, pharmacodynamics, and cumulative toxicity. Before each escalation, investigators will be consulted to ensure that all involved agree with the escalation decision.

Part 2 – Cohort-expansion Phase: Additional patients will be recruited to one of two groups - Group 1: RAS mutant positive AML or MDS; Group 2: RAS mutant negative AML or MDS - to receive treatment at the Recommended Phase 2 Dose (RP2D). Patients will receive twice daily oral doses of BVD-523 in 21-day treatment cycles until disease progression, unacceptable toxicity, or another withdrawal criterion is met. Treatment cycles will occur consecutively without interruption except when necessary to manage adverse events.

Study Population- Criteria for Inclusion:

Patients eligible for inclusion in this trial must fulfill all of the following criteria:

1. Provide signed and dated informed consent prior to initiation of any study-related procedures that are not considered Standard of Care (SOC).
2. Male or female patients aged ≥ 18 years.
3. Have either of the following diagnoses:
   a. Morphologically confirmed AML (except acute promyelocytic leukemia (APL)) including leukemia secondary to prior therapy (e.g., chemotherapy, radiation therapy (XRT)) or antecedent hematologic disorder (e.g., MDS or myeloproliferative disorders), who have failed to achieve CR or who have relapsed after prior therapy and are not candidates for potentially curative therapy.
   b. Intermediate-2 or High-grade risk MDS (including chronic myelomonocytic leukemia (CMML)).
4. Have received at least one prior therapy. Patients who are over age 65 and have not received therapy for AML are also eligible, if they are not candidates for induction chemotherapy.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active, able to carry out all pre-disease activities without restriction) to 2 (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours), measured within 72 hours before the start of treatment.
6. Predicted life expectancy of ≥ 3 months.
7. Adequate renal function [creatinine ≤ 1.5 times ULN (upper limit of normal)] or glomerular filtration rate (GFR) of ≥ 50mL/min.
8. Adequate hepatic function [total bilirubin ≤ 1.5 x UNL; AST (aspartate transaminase) or ALT (alanine transaminase) ≤ 3 x UNL or ≤ 5 x UNL if due to liver involvement by tumor].
9. Adequate cardiac function, ≥ institutional lower limit of normal e.g., left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); corrected QT interval (QTc) < 470 ms.
10. Contraception:
    - For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (defined as no menstrual cycle for at least 12 consecutive months), or compliant with an acceptable contraceptive regimen (oral contraceptives, condom with spermicide, etc.) during and for 3 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen.
    - For men: Must be surgically sterile, or compliant with a contraceptive regimen (as above) during and for a minimum of 3 months after the treatment period.
11. Willing and able to participate in the trial and comply with all trial requirements.
12. **For Part 2 Group 1 of the Study ONLY:**
    Positive for RAS mutation at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory prior to study entry.

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Criteria for Exclusion:

Patients who fulfill one or more of the following criteria will not be eligible for inclusion in this trial:

1. Concomitant malignancies except carcinoma in situ, basal or squamous cell skin carcinoma; low grade prostate cancer treated with prostatectomy more than 10 years ago; early stage melanoma treated with complete surgical excision more than 5 years ago; carcinoma in situ of cervix treated with cone procedure more than 8 years ago.
2. Gastrointestinal (GI) condition that could impair absorption of study medication (specific cases e.g., remote history of GI surgery, may be enrolled after discussion with the medical monitor), or inability to ingest study medication. Refractory nausea and vomiting must also be discussed with the Medical Monitor prior to enrolling such a patient.
3. Uncontrolled or severe intercurrent medical condition.
4. Patients with rapidly increasing peripheral blood blast counts (significant increase in the absolute peripheral blast count with white blood cell (WBC) > 30,000) or uncontrolled (absolute blast count > 30,000) while on hydroxyurea will be excluded.
5. Known uncontrolled central nervous system (CNS) involvement. (Stable asymptomatic CNS involvement either untreated or being treated with a stable dose (or doses) of intra-thecal therapy(ies) can be allowed if there is evidence that the CSF cell count is decreased and that patient is responding to IT therapy.)
6. Any cancer-directed therapy (chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives, (whichever is shorter).
7. Any concurrent or prior use of an investigational drug (including MEK inhibitors) within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of BVD-523. A minimum of 10 days between termination of the investigational drug and administration of BVD-523 is required. In addition, any drug-related toxicity except alopecia should have recovered to Grade 1 or less.
8. Received chemotherapy regimens with delayed toxicity within the last four weeks (six weeks for prior nitrosourea or mitomycin C). Received chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last two weeks.
9. Ongoing anticoagulant therapy that cannot be held if necessary to permit bone marrow sampling. Patients who require anticoagulant therapy and cannot be maintained on low molecular weight heparin (LMWH) should not be considered for this study.
10. Major surgery within 4 weeks prior to first dose.
11. Pregnant or breast-feeding women.
12. Any evidence of serious active infections (subjects who have been fever-free for 24 hours prior to enrollment and on active treatment would not be considered excluded).
13. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).
14. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).
15. Concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, or strong inducers of CYP3A4 (for list of non-permitted drugs, see Appendix 1).

Test Product, Dose and Mode of Administration:

Part 1: BVD-523, starting at an oral dose of 300 mg taken with at least 8 ounces of water twice-daily for each 21 day cycle, with escalating dose levels (classic 3+3 design). Dosing of each subject will continue until the subject withdraws from the study or dies. A subject that has a Dose Limiting Toxicity (DLT) may be dose reduced or be withdrawn from the study depending upon the decision of the Safety Monitoring Committee (which includes the Sponsor, Medical Monitor and the study investigator) in Part 1.

Part 2: BVD-523, recommended Phase 2 dose (RP2D), taken orally with at least 8 ounces of water twice-daily

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for each 21 day cycle. Dosing of each subject may continue until the subject is discontinued from the study. A subject that has a Dose Limiting Toxicity (DLT) may be dose reduced or be withdrawn from the study depending upon the decision of the Safety Monitoring Committee (which includes the Sponsor, Medical Monitor and the study investigator).

Concomitant Medications:

Necessary supportive care such as antibiotics, blood product transfusions, antiemetics, antidiarrheals, etc., will be allowed. Drugs that are strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, or strong inducers of CYP3A4, will not be allowed during the study (see Appendix 1).

Study Duration:

Part 1: Approximately 6 months, Part 2: 18 to 24 months

Criteria for Evaluation

Safety:

Vital signs, physical examination, ophthalmology examination, clinical chemistry, hematology, urinalysis, electrocardiograms (ECG). The severity of adverse events (AEs) will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) Grading Scale Version 4.03 (see the NCI CTCAE web page at http://ctep.cancer.gov for details).

Efficacy:

Clinical response will be assessed on results of bone marrow biopsies using International Working Group 2003 and 2006 criteria for AML or MDS respectively (1, 2).

Pharmacokinetics:

Blood samples will be collected to measure BVD-523 and selected metabolite concentrations. At Baseline (Visit 2, Cycle 1) and again on Day 22 (Visit 5, Cycle 1), blood samples will be collected prior to administration of the first daily dose and then post-dosing at the following time points: 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours.

Pharmacodynamics:

Blood and/or bone marrow aspirate will be used to evaluate multiple biomarkers of drug response including pRSK and total RSK. Blood and/or bone marrow aspirate will be collected to measure *ex vivo* BVD-523 sensitivity of leukemic cells prior to therapy on Day 1 and on Day 22 of Cycle 1. Additional biomarkers and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state.

Statistical Methods:

The sample size for Part 1 of this study was determined by clinical rather than statistical considerations. Approximately 20 patients will be treated in Part 1 of this study (Dose Escalation Phase) to establish dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D).

After completion of Part 1 of this study, Part 2 will commence. In Part 2, up to 40 additional AML or MDS patients will be recruited to one of two groups- Group 1: patients with positive RAS mutant AML or MDS and Group 2: patients with negative RAS mutant AML or MDS will be treated with the RP2D of BVD-523. The purpose of the second phase of this study is to document evidence of response. With 20 subjects in each group, there is an 88% probability of seeing at least one positive response in each group if the true response rate is at least 10%.

The observation of DLTs in more than 33% of patients in either Part 2 cohort with at least 6 patients enrolled at any time during Part 2 will trigger temporary stopping of patient enrollment and revision of the definition of the MTD and RP2D in the specific cohort. Subsequent patients will be treated with a dose lower than the initial RP2D and this dose will be determined in discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AMS	acute myelodysplastic syndrome
AMP	adenosine monophosphate
APL	acute promyelocytic leukemia
AST	aspartate transaminase (SGOT)
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
BM	bone marrow
BMI	body mass index
BP	blood pressure
Bpm	beats per minute
BUN	blood urea nitrogen
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
cm	centimeter
C_{max}	maximum concentration
CMC	carboxymethylcellulose
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNS	central nervious system
CPWW	Clinipace Worldwide
CR	complete remission/complete response
CR_p	complete remission with incomplete platelet recovery
CRF	case report form
CSF	cerebrospinal fluid
CSR	central serous retinopathy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP 1A2	cytochrome P450 isoform 1A2
CYP 2D6	cytochrome P450 isoform 2D6
CYP 3A4	cytochrome P450 isoform 3A4
dL	deciliter
DLT	dose limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOS	end-of-study
ERK	extracellular signal-regulated kinase
°F	degrees Fahrenheit
%F	absolute bioavailability
FDA	Food and Drug Administration
FDG-PET	^{18}F-fluorodeoxyglucose-positron-emission tomography
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HCl	hydrochloride
HDL	high-density lipoprotein
hERG	human ether-a-go-go related gene
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IT	intrathecal
ITT	intent-to-treat
kg	kilogram
LD	largest diameter
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
LS	least squares
µg	microgram
m^2	square meters
MAPK	mitogen-activated protein kinase
MDS	myelodysplastic syndrome
MEDDRA®	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase/extracellular signal-related kinase
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multi-gated acquisition

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
NCI	National Cancer Institute
NOEL	no observed effect level
ng	nanogram
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PI	Principal Investigator
PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetics
PT	prothrombin time
PTT	partial thromboplastin time
q.d.	once daily
QT	a measure between Q and T waves in heart electrical system
QT_c	corrected QT interval
QT_cF	Fridericia-corrected QT interval
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors (Version 1.1)
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
RVO	retinal vein occlusion
SAE	serious adverse event
SAS	Statistical Analysis Systems
SCT	stem-cell transplantation
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SEM	standard error of the mean
SMC	Safety Monitoring Committee
TSH	thyroid-stimulating hormone
TTP	duration of response
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WO	washout
WPSS	WHO classification–based Prognostic Scoring System
XRT	radiation therapy

1 INTRODUCTION

A critical hallmark of cancer is the activation of cell-growth signaling cascades independent of appropriate growth stimuli (3). A canonical example of a cell growth control circuit is the mitogen-activated protein kinase, or MAPK, pathway. Here, surface receptors activated by growth ligands signal via downstream effectors in a linear relay system: RAS family GTPases activate RAF family protein kinases, which in turn trigger a phosphorylation cascade involving mitogen-activated protein kinase/extracellular signal-related kinase (MEK) and extracellular signal-regulated kinase (ERK) family kinases. ERK kinases activate an array of direct effectors that ultimately translate growth signaling into essential cellular functions including cell division and cell survival.

Aberrant activation of the MAPK pathway is frequently observed in cancer. Often, components of the MAPK pathway undergo direct genetic mutation, causing constitutive activation of the signaling cascade in the absence of appropriate ligands. For example, members of the RAS GTPase family (KRAS, NRAS, and HRAS) were among some of the first endogenous oncogenes demonstrated to exhibit spontaneous, activating mutations in a variety of cancers, including pancreatic, colorectal and non-small cell lung malignancies (4).

Up-regulation of the Ras>Raf>MEK>ERK and PI3K>Akt pathways and phosphorylation of the downstream target Bad are observed frequently in AML specimens and associated with a poorer prognosis than that seen in patients lacking these changes (5, 6). Aberrant expression of a single pathway is associated with a poor prognosis and abnormal expression of multiple signaling pathways is associated with an even worse prognosis (5). Dysregulation of the Ras>Raf>MEK>ERK and PI3K>Akt pathways in some AMLs may result from constitutive activation of Flt-3 (7, 8, 9). Thus these two signaling pathways provide important clues regarding the mechanisms responsible for autonomous AML growth (10, 11, 12, 13, 14). Targeting these “downstream” pathways may prove effective for AML therapy, including in those cases where the precise mutation responsible for malignant transformation is unknown.

AML is the most common type of acute leukemia seen in adults, with approximately 13,000 cases diagnosed annually in the United States (US). The median age at onset is 67 years, with the majority of patients being between 65 and 84 years at the time of diagnosis (15). The incidence of this hematologic malignancy can be expected to increase as the US population ages. AML is often fatal, with a 5-year survival rate of only 23% (16).

The goal of treatment of AML is to achieve a complete remission by reducing the malignant clone(s) to allow recovery of peripheral blood production and re-population of the bone marrow (BM) with normal hematopoietic stem cells. In the induction treatment of AML, complete remission is considered the only clinically important form of response. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy. In the majority of patients with AML who achieve a complete response (CR), the leukemia will recur within 3 years after diagnosis. In general, the prognosis of patients after relapse is poor and treatment options unsatisfactory (17).

The Ras>Raf>MEK>ERK pathway is also activated by many cytokines which are important in driving the proliferation and promoting the survival of myeloid cells (18). After receptor

ligation, Shc, Src homology (SH)-2, a SH2-domain containing protein, becomes associated with the c-terminus of the cytokine receptor (19, 20, 21). Shc recruits the GTP-exchange complex Grb2/Sos resulting in the loading of membrane bound Ras with GTP (22, 23). Ras:GTP then recruits Raf to the membrane where it becomes activated, likely via a Src-family tyrosine kinase (24, 25, 26). Raf is responsible for phosphorylation of the mitogen associated/extracellular regulated kinase-1 (MEK1) (27, 28, 29). MEK1 phosphorylates extracellular regulated kinases 1 and 2 (ERKs 1 and 2) on specific threonine and tyrosine residues (27, 28, 29).

Activated ERK1 and ERK2 serine/threonine kinases phosphorylate and activate a variety of substrates including p90Rsk1 (30, 31, 32, 33, 34, 35, 36). p90Rsk1 can activate the cyclic-AMP response element binding protein (CREB) transcription factor (33). Moreover, ERK can translocate to the nucleus and phosphorylate additional transcription factors such as Elk1, CREB and Fos which bind promoters of many genes, including IL-3, a cytokine important in stimulating the growth and survival of early myeloid progenitor cells (32, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47). The Raf>MEK>ERK pathway can also modulate the activity of many proteins involved in apoptosis including: Bcl-2, Bad, Bim, Mcl-1, caspase 9, and Survivin (48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58). Therefore, targeting AML cells with an ERK1/2 inhibitor such as BVD-523 may be effective in this difficult to treat patient population.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by a hypercellular bone marrow, peripheral cytopenias, and morphologic dysplasia in erythroid cells, neutrophils and their precursors, and megakaryocytes. A diagnosis of MDS is made based on the identification of dysplasia in at least 10% of cells of any of the myeloid lineages in the peripheral blood/bone marrow after exclusion of acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) (59). The median age at diagnosis is 71 years (60). It is estimated that the current incidence of MDS in the United States (US) is approximately15,000 to 20,000 cases; however, given that MDS was not a reportable cancer to the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database until 2002, it is considered likely that the actual incidence is as much as 7-8-fold higher (61).

Several prognostic scoring systems are used to categorize MDS, with higher risk categories having shorter median survival and higher risk of progression to AML. The most widely used prognostic scoring system is the International Prognostic Scoring System (IPSS), which classifies patients into lower risk categories (low and intermediate-1) and higher-risk categories (intermediate-2 and high) (62). Risk category is calculated based on the percentage of blasts, number of cytopenias, and bone marrow cytogenetics. Median survival in the IPSS intermediate-2 and high-risk categories is short (1.1 and 0.4 years, respectively). Another prognostic tool, the World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS), incorporates morphological disease characteristics, IPSS cytogenetics, and red cell transfusion needs, and categorizes patients into 5 risk categories ranging from very-low risk to very-high risk. Median survival in the very-low risk category is 103 months and is notably shorter (12 months) in the very high-risk category. Furthermore, patients in the very-high risk category have a high risk of transformation to AML), whereas the risk is low (0.06%) of transformation to AML for the very low-risk group (63). Overall, it is estimated that approximately 30% of patients with MDS will progress to AML.

Goals of therapy for high-risk MDS include prolongation of overall survival as well as prolongation of time to progression to AML. Three novel agents have relatively recently been approved in the US for the treatment of MDS (azacitidine, decitabine, and lenalidomide); however, allogeneic hematopoietic stem-cell transplantation (SCT) remains the only known curative procedure (64).

Similar to AML, the MAPK/ERK pathway is activated in hematopoietic stem cells in MDS patients. Therefore, investigational agents targeting other MAPK components are being explored in both monotherapy and combination chemotherapy regimens. For example, inhibitors of MEK family kinases have shown preliminary signs of clinical efficacy in BRAF-mutant melanoma, and may also prove effective in cancers where RAS GTPase activating mutations are present (65, 66, 67).

The ERK family kinases are MAPK signaling components that have yet to be therapeutically targeted. BVD-523 is a small-molecule inhibitor of ERK kinases that we plan to test in various treatment settings. Understanding the safety and efficacy of BVD-523 will bolster the armamentarium of targeted therapies that can be used against the activated MAPK signaling pathway in hematologic malignancies.

1.1 STUDY DRUG

BVD-523 is a small molecule that potently inhibits both ERK1 and ERK2 protein kinases in the sub-nanomolar range, while not significantly inhibiting any of an array of kinases even at 1000-fold greater concentrations. BVD-523 potently inhibits growth and survival in cultured cancer cell lines; melanoma, colorectal and pancreatic lines harboring BRAF or RAS mutations are among those most susceptible to the drug. In animals bearing ectopic tumor xenografts, orally administered BVD-523 is effective as a single agent, again preferentially in cancers where activating mutations in the MAPK pathway cause abundant ERK kinase activation.

BVD-523 will be administered orally in humans. The HCl salt of BVD-523 was selected for manufacture of drug product in capsule form.

More information is available in the Investigator's Brochure for BVD-523.

1.2 INDICATION

Initial indications for BVD-523 are advanced solid and hematologic malignancies, especially those known to harbor activating genetic mutations in components of the MAPK pathway such as the BRAF or MEK kinases, or members of the RAS GTPase family. Given this biological rationale and relevant preclinical supportive data, AML or MDS are potential indications for development.

1.3 BACKGROUND TO THE DISEASE

Contemporary cancer therapy seeks to leverage a molecular level understanding of disease to rationally target isolated cancer types, often with agents specifically designed to correct well-characterized cellular, biochemical or genetic aberrations. The modern view of cancer as a fundamentally genetic disease has greatly aided the invention and development of several such "targeted" therapies.

A unique array of oncogenic mutations cluster in the mitogen-activated protein kinase (MAPK) pathway, a key signal transduction cascade that controls cell-growth signaling in many tissues (70, 71, 72, 73, 74). As described in detail previously in the Introduction, the MARK/ERK pathway is activated in hematopoietic stem cells of both AML and MDS patients. Therefore, investigational agents targeting other MAPK components are being explored in both monotherapy and combination chemotherapy regimens. Activating mutations in RAS GTPase family members are found in ~30% of all cancers (75). The inhibitors of the MEK family of kinases have shown preliminary signs of clinical efficacy in BRAF-mutant melanoma and may also prove effective in cancers like AML or MDS where the RAS GTPase activating mutations are present (65, 66, 67).

Less frequently, activating mutations have also been observed in MEK family kinases, which are the direct substrates of RAF kinases. MEK kinases phosphorylate and activate the ERK kinase gene family. ERK kinases phosphorylate numerous proteins that act as MAPK pathway "effectors"; these substrates directly promote cell division, reduce cell death, and increase cell motility and cell differentiation (68, 69). To date, spontaneous activating mutations in ERK kinases have not been observed in human cancers. Nonetheless, abundant ERK phosphorylation reflecting elevated MAPK signaling is frequently observed in cancer contexts where extracellular growth factors are elevated or where activating mutations in RAS, BRAF, or MEK genes have occurred (74).

In this setting, therapies targeted against MAPK pathway components have been rationally applied in cancers that show activation of the signaling cascade following genetic mutation. Notably, vemurafenib (ZELBORAF®) is an inhibitor of mutated BRAF that, when dosed in patients with metastatic melanoma harboring specific BRAF activating mutations, for example, induces tumor regression and improves overall survival in this defined patient population (75, 76, 77).

The development of additional therapies that can modulate the MAPK pathway activity in cancer is desirable for several reasons. First, all drugs exhibit a unique spectrum of side effects that often influences their therapeutic utility. Despite some findings suggestive of mechanism-related events, the incidence and severity of both BRAF and MEK inhibitor associated toxicities may uniquely indicate their use in particular patients. Likewise, given the potential for drug-drug interactions, and an increasing emphasis on polypharmacy in targeted oncology regimens, it is desirable to have multiple unique agents with discrete pharmacology and prescribing characteristics, even when they may share a common, redundant target or modes of inhibition in a pathway.

Additionally, a more fundamental and prominent problem drives the need for additional MAPK pathway modulators: increasingly, multiple inhibitors in the pathway exhibit the phenomenon of acquired drug resistance (78, 79, 80, 81). Acquired resistance may limit the clinical efficacy of MAPK directed agents even when their initial activity is promising. The severe consequences and complex biology of acquired resistance in patients treated with MAPK signaling inhibitors suggest that additional, novel agents targeting the pathway may display improved durability and overall efficacy (81).

Given this background, we plan to assess the safety and efficacy of BVD-523, which is a potent and selective inhibitor of the ERK family kinases. Drugs targeting other components of the

MAPK pathway exhibit promising therapeutic activity, while also being limited by unique toxicities and limited duration of efficacy. Targeting the downstream MAPK kinase, ERK, could possibly evoke a unique and desirable balance of durable efficacy and suitable tolerability. As such, BVD-523 may represent a valuable addition to the armamentarium of drugs useful for treating patients whose cancers exhibit the hallmarks of aberrant MAPK pathway activity.

1.4 PREVIOUS HUMAN EXPERIENCE

This study will be the second study conducted with BVD-523 in humans. The first study, Protocol BVD-523-01, "Phase 1 Dose-escalation, safety, pharmacokinetic and pharmacodynamics study of BVD-523 in patients with advanced malignancies", is in progress. Twenty seven patients with advanced malignancies have been treated in the dose-escalation part (Part 1) of the first-in-man Phase 1 clinical study to investigate the safety of BVD-523 and define the MTD and the recommended Phase 2 dose (RP2D). The dose escalation phase included dose levels of 10, 20, 40, 75, 150, 300, 600, 750, and 900 mg b.i.d. The MTD and RP2D of BVD-523 was established to be 600 mg b.i.d (82).

The most common adverse events included diarrhea, nausea, vomiting or constipation (89%), rash (any form), dermatitis, or pruritus (78%), fatigue (70%), decreased appetite (37%), dyspnea (33%), and anemia (26%). Pharmacokinetics were generally linear and dose proportional up to 600 mg twice a day, and BVD-523 achieved pharmacologically relevant exposure (82).

1.5 PRECLINICAL DATA

In this section a short summary of preclinical data is provided. Detailed information is presented in the BVD-523 Investigator's Brochure (Version 2.0, 21 April 2014).

1.5.1 Potential Risk

Preliminary evidence from *in vitro* and *in vivo* toxicological assessments of BVD-523 and data to-date from the first-in-human study (BVD-523-01) suggests the molecule has a safety profile supportive of its development as an anti-cancer therapeutic. Additionally, human clinical trials have been conducted using other drugs known to affect the MAPK pathway and findings from these studies may provide information regarding possible safety risks that may be mechanistically attributable to MAPK pathway inhibition.

Thus, the risk profile for BVD-523 may potentially include the following:

Dermatological Lesions

Dermatological lesions have been seen in rodent GLP toxicology studies of BVD-523. Several of the following findings displayed exposure-dependent increases in incidence and/or severity: non-specific dermal inflammation, pustular dermatitis, epidermal ulceration and acanthosis. These toxicities appeared to be associated with predominantly reversible pharmacodynamics, as the majority of findings were mild and/or of low incidence in animals that underwent dose cessation.

In clinical studies, other drugs that inhibit components of the MAPK pathway exhibit cutaneous toxicity. Multiple investigational inhibitors of MEK1/2 kinases exhibit exposure- dependent,

dose-limiting and reversible skin toxicities in a proportion of patients. Specific toxicities include: non-specific rash and pruritus, acneiform dermatitis, epidermal fissure, and paronychia. Additionally, clinical experience with both investigational agents and approved drugs that primarily target BRAF kinase have displayed exposure-dependent and reversible skin toxicities in a proportion of treated patients; relevant lesions here include keratoacanthoma-type squamous cell carcinomas, non-cancerous hyperkeratosis and actinic keratosis.

A similar pattern of cutaneous toxicity was observed in the first 18 patients in Part 1 of the first study, Protocol BVD-523-01, with two-thirds of patients experiencing rash and one patient with a history of squamous cell carcinoma developing a squamous cell carcinoma while on treatment with BVD-523. Rash has been treated with topical and/or oral agents (e.g., steroids), and dose reductions/interruptions as needed.

Phototoxicity

BVD-523 exhibits an absorbance peak in the range of UV-A/UV-B light, specifically at ~320 nm. Clinical studies of other drugs that modulate MAPK pathway components have exhibited skin phototoxicity.

Beyond dermatological monitoring (above), potential risks of direct phototoxicities induced by BVD-523 will be reduced by advising that patients minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients will be informed that relevant sun exposure may occur even through glass, such as while driving.

Ophthalmological Effects

Preclinical toxicology studies of BVD-523 have not revealed any exposure-dependent ophthalmological toxicities; however, clinical studies of MEK1/2 kinase inhibitors highlight ocular toxicities that may reflect mechanistically attributable risks observable in a proportion of patients. Of particular concern are the following dose-limiting toxicities comprising exposure-dependent, serious adverse events during clinical studies: retinal vein occlusion, retinal detachment and related vision abnormalities. In the ongoing first-in-man Phase 1 study, thru 1-April-2014, a single AE of vision changes has been reported in a single patient on a low dose of BVD-523 (20 mg, b.i.d.). While it is not definitively understood whether ocular toxicities reflect primary pharmacology associated with global inhibition of the MAPK pathway, specific management and exclusion criteria are defined in this clinical protocol, as the toxicities could potentially severely and irreversibly impact patient well-being.

Gastrointestinal Toxicity

Preclinical toxicity studies of BVD-523 have provided evidence of exposure-related, reversible gastrointestinal toxicities, and these toxicities have also been observed at high frequency in the first 18 patients in the ongoing first-in-man Phase 1 study of advanced malignancies (Protocol BVD-523-01), in once case leading to an SAE of renal insufficiency secondary to dehydration. The severity and reversibility of these non-clinical and clinical toxicities, while not meriting a specific monitoring or treatment plan, warrant active routine monitoring of patients for this toxicity.

QTc Prolongation

The balance of preclinical evidence suggests BVD-523 has low, but observable, potential to cause QT prolongation. Due to potentially unique species sensitivity, as well as possibly unknown consequences following chronic dosing, patients dosed with BVD-523 in the first-in-human study, BVD-523-01, are being monitored for potential QTc prolongation and related cardiotoxicities via Holter monitoring. No clinically significant cardiac abnormalities have been seen to date in the first trial (BVD-523-01). QTc assessment will be performed at baseline and on Day 8, at steady state.

Tissue Mineralization

Tissue mineralization has been observed in rodent toxicology studies of BVD-523. The incidence and severity of mineralization was dose-dependent and effects were observed in one or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen. These effects were not observed in animals in which there was no mineralization.

Tissue mineralization has been reported in rodents with other compounds that target the MAPK pathway and published studies suggest that the MAPK pathway is a negative regulator of matrix mineralization both *in vitro* and *in vivo*.

Routine clinical laboratory tests, including blood chemistry analyses for calcium and inorganic phosphate, will be performed and any indication of abnormalities may result in further investigations. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway.

Hematological Effects

Hematological effects observed in a rat repeat dose study included lowered reticulocyte counts, mean corpuscular volume, platelet counts (in females only) and increased neutrophil, monocyte, basophil and large unstained cell counts. In dogs the clinical pathology findings were consistent with inflammation (increased white blood cell count, neutrophils, fibrinogen and globulin) and decreased albumin and hemorrhage (decreased red cell mass).

In order to monitor for potential hematologic toxicity in humans, routine clinical laboratory hematology tests, should be performed and any indication of abnormalities may result in further investigations.

1.5.2 Pharmacology Studies

BVD-523 is highly efficacious *in vivo* when administered as a single agent in ectopic xenograft models of colon, pancreatic and melanoma cancers, 3 tumor types in which ERK is known to be highly activated. Notably, partial regression was achieved in a colon cancer model (Colo205) when the compound was administered at 50 mg/kg (b.i.d.). Biomarker analyses confirmed that improved efficacy obtained at higher doses of BVD-523 correlated with increasing ERK inhibition.

1.5.3 Toxicity and Safety Studies

When BVD-523 was characterized using *in vitro* screens against 66 receptors and ion channels, no toxicologically significant interactions were identified. Additionally, BVD-523 was negative in bacterial mutation and *in vivo* micronucleus screening assays; therefore, BVD-523 is not considered to have a significant genetic toxicology risk.

While BVD-523 modestly inhibits the human ether-a-go-go related gene (hERG) current (IC_{50} 3.4 μM), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10 μg/mL and no significant cardiovascular findings were observed upon acute oral dosing of the compound at dose levels up to 50 mg/kg in dogs (C_{max} = 17.3 μM). Thus BVD-523 is considered to have a low potential to cause QT prolongation in patients, but, as stated, the first-in-human study will monitor for signs of cardiovascular effects of BVD-523 in humans.

No significant cytochrome P450 (CYP) inhibition has been observed with the compound.

In vitro studies suggest that the compound is metabolized primarily via oxidation by multiple CYPs including 3A4, 2D6, and 1A2. Furthermore, no significant CYP induction was observed after up to 14 days drug treatment in rats, nor during *in vitro* studies with human hepatocytes. These data suggest a limited potential for drug-drug interactions.

BVD-523 HCl salt is orally available in multiple species (absolute bioavailability %F = 23% in dog to 100 % in monkey) when formulated as a simple suspension in 1% carboxymethyl-cellulose (CMC) and has a half-life of 2-4 hours across all species.

BVD-523 was administered to male and female Sprague-Dawley rats in several toxicology studies: (1) a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; (2) for up to 14 days at dose levels up to 100 mg/kg twice daily; and (3) for up to 5 days at dose levels up to 150 mg/kg/dose once daily. The incidence and severity of mineralization seen in these studies was dose-dependent and effects were observed in one or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen. These effects were not observed in animals in which there was no mineralization. Therefore, the risk of tissue mineralization can be assessed by serum phosphorus and calcium monitoring. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway because those compounds likewise elicited mineralization in rodents.

When BVD-523 was administered to male and female Sprague-Dawley rats for up to 28 days at a dose level of 25 or 50 mg/kg twice daily, BVD-523 was poorly tolerated. Although most clinical signs and clinical pathology findings reversed following 4 weeks of recovery, skin lesions and histopathology findings persisted in many tissues at both dose levels after the recovery. Based on these findings, 25 and 50 mg/kg twice daily dose levels were considered severely toxic. Administration of 12.5 mg/kg twice daily for 28 days was generally well-tolerated by rats of both sexes; however, this dose level was associated with test article-related findings that included (1) swelling in the neck, (2) decreased forelimb strength, (3) multiple clinical pathology findings, and (4) enlarged lymph nodes, spleen, and mammary gland. Based on these observations, the severely toxic dose in 10% of the animals (STD10) for BVD-523

when administered for up to 28 days in Sprague-Dawley rats is 12.5 mg/kg given twice daily (25 mg/kg/day). On Day 28 of the dosing phase, this dose level corresponded with a C_{max} of 28700 and 15323 ng/mL and AUC_{0-12} of 264868 and 124341 hr.ng/mL for males and females, respectively.

BVD-523 was administered to male and female beagle dogs for up to 28 days at dose levels of 15, 5, or 2 mg/kg twice daily. Initial analysis of the toxicity profile observed shows that BVD-523 was well tolerated in dogs. The rat was designated the most sensitive species and rat data were used to calculate the starting dose in man.

Based on the data accumulated to date, BVD-523 possesses a toxicology profile which presents no impediment to its development as an anti-cancer agent.

For further information, please refer to the BVD-523 Investigator's Brochure (Version 2.0, 21 April 2014).

2 RATIONALE FOR THE STUDY

The overall purpose of this study is to support the development of an oral formulation of BVD-523 for the treatment of patients with AML or MDS. BVD-523 is a highly potent, selective, and pharmacologically active inhibitor of ERK family kinases. The compound has demonstrated efficacy as a single agent in preclinical models of colon, pancreatic and melanoma cancers (Section 1.5.2), and has potential for application alone or in combination with existing cancer chemotherapeutics.

This study is being performed to assess the safety, tolerability, and preliminary clinical effects of BVD-523 given orally, twice daily for 21-day cycles, in patients with AML or MDS. The pharmacokinetics and pharmacodynamics of BVD-523 will also be explored after the first doses administered on Day 1 and at steady state on Day 22. Subsequent assessments may be done as indicated after completion of Cycle 1.

2.1 RATIONALE FOR THE DOSES AND THE DOSING REGIMEN

The human Phase 1 starting dose for BVD-523 in the first trial (BVD-523-01) was derived from 28-day GLP toxicology studies performed in rodent and non-rodent species and calculated as described by Senderowicz (83). Specifically, our results indicated that toxicity in rodents would be used to establish starting dose in patients. The severely toxic dose in 10% of the animals (STD10) for BVD-523 when administered for up to 28 days in Sprague-Dawley rats was determined to be 12.5 mg/kg dosed twice daily (25 mg/kg/day). A standard 10-fold reduction of this dose was scaled to establish a starting dose of 13.5 mg twice-daily of BVD-523 (free base equivalents) or 14.6 mg twice-daily of BVD-523, based on an average body surface area of 1.8 m^2 consistent with current clinical practice and dosing convenience, the proposed starting dose for the first Phase 1 clinical study with BVD-523 in cancer patients (BVD-523-01) was 10 mg twice-daily (20 mg/day) (84).

The starting dose determination for this Phase 1/2 study (BVD-523-02) in AML or MDS patients described herein is based on the clinical experience during the dose-escalation study in patients with solid tumors. The dose escalation phase of study BVD-523-01, the first-in-man Phase 1 clinical study included 27 patients treated at dose levels of 10, 20, 40, 75, 150, 300, 600, 750, and 900 mg b.i.d. DLTs were observed in 5 pts: 2 with grade 3 rash (600 mg and 750 mg b.i.d.), 1 with grade 3 pruritus and elevated AST (900 mg b.i.d.), 1 with grade 3 diarrhea, vomiting, dehydration and elevated creatinine (900 mg b.i.d.), and 1 with grade 2 hypotension, elevated creatinine, and anemia (750 mg b.i.d.); the MTD was established at 600 mg b.i.d. BVD-523 achieved pharmacologically relevant exposure and manageable tolerability at its MTD of 600 mg b.i.d (82). *Ex vivo* whole blood assays demonstrated inhibition of phosphorylation of RSK, a downstream substrate of the target ERK, at doses ≥ 40 mg, b.i.d. Additionally, inhibition of metabolic activity was demonstrated by FDG-PET at 75 mg, b.i.d. The 300 mg b.i.d. starting dose for the BVD-523-02 study with AML or MDS patients is based upon these results in the solid tumor study. As the ongoing Phase 1 study progresses, the 300 mg b.i.d. starting dose in AML or MDS patients may be revised based upon accruing safety experience and determination of the RP2D from the solid tumor study.

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

This is an open-label, multi-center Phase 1/2 study with a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2) in patients with Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS). This study will be conducted at up to 6 study centers.

3.1.1 Study Objectives

3.1.1.1 Primary Objectives

- To define the safety and tolerability of BVD-523 in patients with AML or MDS determining the dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).
- To determine the pharmacokinetic profile of BVD-523 and selected metabolites in patients with AML or MDS.

3.1.1.2 Secondary Objectives

- To assess clinical response in patients with AML or MDS treated with BVD-523 at the recommended Phase 2 dose (RP2D).
- To determine the progression-free survival (PFS) and duration of response (DOR) of AML or MDS patients treated with BVD-523 achieving CR/CRp.

3.1.1.3 Exploratory Objective

- To evaluate pharmacodynamic marker (biomarker) measures.

3.1.2 Methodology / Study Design

BVD-523-02 is an open-label, multicenter, Phase 1/2 study with a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2).

Part 1 Dose-escalation Phase:

A classic "3+3" design will be used to establish dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). Three to six patients per treatment cohort will be assigned to receive sequentially higher oral doses of BVD-523 on a twice daily schedule (b.i.d.) for 21 days (a "Cycle"), starting at a dose of 300 mg twice daily. Patients will receive twice-daily oral doses of BVD-523 until disease progression, unacceptable toxicity, or a clinical observation satisfying another withdrawal criterion is noted. Treatment cycles will occur consecutively without interruption, except when necessary to manage adverse events. All dose-escalation decisions will be based on Cycle 1 safety data and doses will not be escalated unless the patients receiving the highest current dose have been observed for at least 21 days (1 cycle).

The classic 3 + 3 design will be conducted as follows. Initially, 3 patients will be enrolled to a cohort; the occurrence of a single drug-related DLT in one of these 3 patients will prompt enrollment of up to 3 additional patients to that same cohort. When more than 1 DLT occurs in

≤ 6 patients in a dosing cohort, dose escalation will be stopped and this dose level will be identified as the non-tolerated dose.

Doses between the non-tolerated dose and the preceding lower dose, where ≤ 1 DLT occurred, may be explored to more precisely define the MTD. This strategy allows for a rigorous determination of MTD, especially if the dose increase that resulted in determination of the non-tolerated dose is relatively large (i.e., > 50%).

During the study, the Safety Monitoring Committee may request that cohorts be enlarged or that evaluation of intermediate doses between 2 planned escalation steps be explored. Such requests will be discussed with the Investigator(s), Sponsor and Medical Monitor, and should be based on all data existing at that time, including safety and clinical activity, determinations of pharmacokinetics, pharmacodynamics, and cumulative toxicity. Before each escalation, investigators will be consulted to ensure that all involved agree with the escalation decision.

In addition, intra-patient dose escalation will be allowed after a patient has completed at least one cycle at their assigned dose, with escalation up to a dose where at least 3 patients have completed at least one cycle.

Part 2 Cohort-expansion Phase:

Additional patients with AML or MDS with or without specific genetic mutations indicative of MAPK pathway activation will be recruited for treatment at the Recommended Phase 2 Dose (RP2D). Patients will receive twice daily oral doses of BVD-523 in 21-day treatment cycles until disease progression, unacceptable toxicity, or another withdrawal criterion is met. Treatment cycles will occur consecutively without interruption except when necessary to manage adverse events.

Total enrollment for Part 2 is targeted at approximately 40 patients. Patients will be enrolled into 1 of 2 treatment groups. Group assignments are made according to the following disease characteristics, which correspond to specific inclusion and exclusion criteria for Part 2:

- Group 1: patients with RAS mutant positive AML or MDS; n (evaluable) ≤ 20
- Group 2: patients with RAS mutant negative AML or MDS; n (evaluable) ≤ 20

Table 3.1 Study Medication Dosing and Pharmacokinetics/Pharmacodynamics Chart

	Study Days			
	1	**8± 1**	**15± 1**	**22± 1**
BVD-523 dosing[a]	X	X	X	X
Pharmacokinetics	X			X
Pharmacodynamics	X			X

[a] Dosing is twice daily in 21-day cycles until disease progression. Patients will take their study medication in the clinic on PK days. Patients may be treated beyond disease progression for additional 21-day cycles at the same or escalated dose level (see intra-patient dose escalation Sec 3.1.3) at the Investigator's discretion. Study medication for a week of dosing should be dispensed at each visit for treatment Cycles 1 and 2. For treatment cycles after Cycle 2, study medication will be dispensed to support the entire 3 week cycle.

3.1.3 Summary of Dose Escalation

Table 3.2 Summary of Dose Escalation

Observed Safety Outcomes	Action
1 DLT in 3 patients	Expand cohort up to 6 patients
1 DLT in 6 patients	Escalate by ≤ 50% to next dose level
> 1 DLT in ≤ 6 patients	Stop dose escalation

Note: DLT is defined in detail in Section 3.1.4.2 below.

Each cohort can only begin when the previous cohort has completed treatment to at least the end of Cycle 1 without fulfilling a criterion which would prevent dose escalation. Intra-patient dose escalation will be permitted with consensus among the Principal Investigator, Medical Monitor, and Sponsor, to a dose not to exceed that for which 21 days of treatment has been deemed safe.

Although dose escalation decisions will be taken upon review of the data from Cycle 1, safety data will also be collected from all patients continuing treatment and these data will be reviewed periodically by the Safety Monitoring Committee. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, including having an effect on the RP2D.

3.1.4 Definition of MTD, DLT, and RP2D

3.1.4.1 Definition of Maximum Tolerated Dose (MTD)

MTD is defined as the highest dose cohort at which < 33% of patients experience BVD-523 related DLTs in the first 21 days of treatment.

3.1.4.2 Definition of Dose Limiting Toxicity (DLT)

The DLT is defined using the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0) in the first 21 days of treatment. All toxicities will be considered related to BVD-523 if they cannot be definitively explained by underlying disease, intercurrent illness or concomitant medications.

- Any treatment emergent study drug related Grade 3 or Grade 4 non-hematologic toxicity unless clearly and incontrovertibly unrelated to BVD-523. Exceptions are Grade 3 or 4 nausea or vomiting that is controllable by anti-emetics or Grade 3 or 4 diarrhea controllable by optimal therapy such as loperamide. Grade 3 laboratory investigations other than serum creatinine, bilirubin, AST or ALT will not be considered a DLT unless they are associated with clinical manifestations.
- Study-drug related Grade 4 thrombocytopenia that was not present at study entry and that does not resolve within 7 days, unless clearly and incontrovertibly unrelated to BVD-523.
- Febrile neutropenia or Grade 4 neutropenia that was not present at study entry and that does not resolve within 7 days, unless clearly and incontrovertibly unrelated to BVD-523.
- Prolonged myelosuppression or pancytopenia with a hypocellular bone marrow and no marrow blasts lasting for 6 weeks or more that is not related to disease progression.

- Any study drug related toxicity that results in treatment delays of > 4 days, except when patient is experiencing rash in which case, patient may be off drug for up to 7 days while receiving treatment.

All subjects who are not evaluable for toxicity in Cycle 1 due to unrelated AEs will be replaced.

3.1.4.3 Definition of Recommended Phase 2 Dose (RP2D)

The Recommended Phase 2 Dose (RP2D) may be as high as the MTD and will be determined in discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor. Observations related to pharmacokinetics, pharmacodynamics, and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D.

3.2 SAFETY MONITORING COMMITTEE

An internal Safety Monitoring Committee (SMC) will be set up to review the safety of BVD-523 as the study progresses. The SMC will consist of Clinical Investigators, the Medical Monitor and Sponsor representatives. The SMC will review any serious Adverse Event (SAE) that occurs during the study and will examine the safety of each dose level of BVD-523, including toxicities that may occur in later cycles of treatment.

3.3 SAFETY REVIEW MEETINGS

The safety review will be performed in all stages of the dose escalation:

- Prior to starting each new dose level after the initial cohort.
- To stop the dose escalation if the MTD has been reached.
- An update on patient status will be provided to each investigator semi-monthly.

3.4 STOPPING RULES

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 7: Discontinuation Criteria.

3.5 CRITERIA FOR EVALUATION

3.5.1 Safety

- Vital signs
- Physical examination
- Ophthalmology examination
- Clinical chemistry
- Hematology
- Urinalysis
- ECGs
- Severity of AEs (graded according to the NCI CTCAE Grading System Version 4.03 as detailed on web page: http://ctep.cancer.gov).

3.5.2 Efficacy

- Clinical response will be assessed on results of bone marrow biopsies using International Working Group 2003 and 2006 criteria for AML or MDS, respectively (1, 2).

3.5.3 Pharmacokinetics

- Blood samples will be collected to measure BVD-523 and selected metabolite concentration levels.
- At Baseline (Visit 2, Cycle 1) and again on Day 22 (Visit 5, Cycle 1), blood samples will be collected prior to administration of the first dose and then post-dosing at the following time points: 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours.

3.5.4 Pharmacodynamics

- Blood and/or bone marrow aspirate will be used to evaluate multiple biomarkers of drug response including pRSK and total RSK. Blood and/or bone marrow aspirate will be collected to measure *ex vivo* BVD-523 sensitivity of leukemic cells prior to therapy on Day 1 and Day 22. Additional biomarkers and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state.

3.6 BLINDING AND RANDOMIZATION

This study is designed as an open-label study. All patients will receive treatment with orally administered BVD-523.

4 SELECTION OF PATIENTS

4.1 NUMBER OF PATIENTS

In this study, up to approximately 20 patients with AML or MDS, regardless of RAS mutation status, will be enrolled in Dose-escalation Part 1. Three to six patients per treatment cohort will be assigned to receive sequentially higher oral doses of BVD-523.

In the Cohort-expansion Part 2, additional patients with RAS mutant positive AML or MDS and RAS mutant negative AML or MDS will be recruited for treatment at the RP2D determined from Part 1 above.

Part 2 patients will receive twice daily oral doses of BVD-523 in 21-day treatment cycles until disease progression, unacceptable toxicity, or another withdrawal criterion is met. Treatment cycles will occur consecutively without interruption except when necessary to manage AEs.

Total enrollment for Part 2 is targeted for up to approximately 40 patients. Patients will be enrolled into 1 of 2 treatment groups. Group assignments are made according to the following disease characteristics:

- Group 1: Patients with RAS mutant positive AML or MDS; n (evaluable) $\leq$ 20
- Group 2: Patients with RAS mutant negative AML or MDS; n (evaluable) $\leq$ 20.

4.2 RECRUITMENT

This study will be conducted at up to 6 sites. The study centers will enroll up to approximately 20 patients for Part 1 and up to approximately 40 additional patients for Part 2 of this study.

4.3 INCLUSION CRITERIA

Patients eligible for inclusion in this trial must fulfill all of the following criteria:

1. Provide signed and dated informed consent prior to initiation of any study-related procedures that are not considered Standard of Care (SOC).
2. Male or female patients aged $\geq$ 18 years.
3. Have either of the following diagnoses:
   - Morphologically confirmed AML (except acute promyelocytic leukemia (APL)) including leukemia secondary to prior therapy (e.g., chemotherapy, XRT) or antecedent hematologic disorder (e.g., MDS or myeloproliferative disorders), who have failed to achieve complete remission (CR) or who have relapsed after prior therapy and are not candidates for potentially curative therapy.
   - Intermediate-2 or High-grade risk MDS (including chronic myelomonocytic leukemia (CMML)).
4. Have received at least one prior therapy. Patients who are over age 65 and have not received therapy for AML are also eligible, if they are not candidates for induction chemotherapy.
5. ECOG performance status of 0 (fully active, able to carry out all pre-disease activities without restriction) to 2 (ambulatory and capable of all self-care but unable to carry out

any work activities. Up and about more than 50% of waking hours), measured within 72 hours before the start of treatment.

6. Predicted life expectancy of ≥ 3 months.
7. Adequate renal function [creatinine ≤ 1.5 times ULN (upper limit of normal)] or GFR of ≥ 50mL/min.
8. Adequate hepatic function [total bilirubin ≤ 1.5 x UNL; AST (aspartate transaminase) or ALT (alanine transaminase) ≤ 3 x UNL or ≤ 5 x UNL if due to liver involvement by tumor].
9. Adequate cardiac function, ≥ institutional lower limit of normal, e.g., left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); corrected QT interval (QTc) < 470 ms.
10. Contraception:
    - For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (defined as no menstrual cycle for at least 12 consecutive months), or compliant with an acceptable contraceptive regimen (oral contraceptives, condom with spermicide etc.) during and for 3 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen.
    - For men: Must be surgically sterile, or compliant with a contraceptive regimen (as above) during and for 3 months after the treatment period.
11. Willing and able to participate in the trial and comply with all trial requirements.
12. **For Part 2 Group 1 of the Study ONLY:**

    Positive for RAS mutation at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory prior to study entry.

4.4 EXCLUSION CRITERIA

Patients who fulfill 1 or more of the following criteria will not be eligible for inclusion in this trial:

1. Concomitant malignancies except carcinoma in situ, basal or squamous cell skin carcinoma; low grade prostate cancer treated with prostatectomy more than 10 years ago; early stage melanoma treated with complete surgical excision more than 5 years ago; carcinoma in situ of cervix treated with cone procedure more than 8 years ago.
2. Gastrointestinal (GI) condition that could impair absorption of study medication (specific cases e.g., remote history of GI surgery, may be enrolled after discussion with the medical monitor), or inability to ingest study medication. Refractory nausea and vomiting must also be discussed with the Medical Monitor prior to enrolling such a patient.
3. Uncontrolled or severe intercurrent medical condition.
4. Patients with rapidly increasing peripheral blood blast counts (significant increase in the absolute peripheral blast count with white blood cell (WBC) count > 30,000) or uncontrolled (absolute blast count > 30,000) while on hydroxyurea will be excluded.
5. Known uncontrolled central nervous system (CNS) involvement. (Stable asymptomatic CNS involvement either untreated or being treated with a stable dose (or doses) of intra-

thecal (IT) therapy can be allowed if there is evidence that the cerebrospinal fluid (CSF) cell count is decreased and that patient is responding to IT therapy.)

6. Any cancer-directed therapy (chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives, (whichever is shorter).
7. Any concurrent or prior use of an investigational drug (including MEK inhibitors) within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of BVD-523. A minimum of 10 days between termination of the investigational drug and administration of BVD-523 is required. In addition, any drug-related toxicity except alopecia should have recovered to Grade 1 or less.
8. Received chemotherapy regimens with delayed toxicity within the last four weeks (six weeks for prior nitrosourea or mitomycin C). Received chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last two weeks.
9. Ongoing anticoagulant therapy that cannot be held to permit bone marrow sampling. Patients who require anticoagulant therapy and cannot be maintained on LMWH should not be considered for this study.
10. Major surgery within 4 weeks prior to first dose.
11. Pregnant or breast-feeding women.
12. Any evidence of serious active infections (subjects who have been fever-free for 24 hours prior to enrollment and on active treatment would not be considered excluded).
13. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).
14. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).
15. Concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6 and CYP3A4, or strong inducers of CYP3A4 (for list of non-permitted drugs, see Appendix 1).

5 STUDY PLAN AND PROCEDURES

This clinical study will consist of 2 parts. In Part 1, patients with AML or MDS will receive sequentially higher oral doses of BVD-523.

Upon completion of Part 1 of this study and determination of RP2D, up to approximately 40 additional AML or MDS patients with and without RAS mutation will be treated at the RP2D.

To characterize the pharmacokinetic properties of BVD-523 in patients with AML or MDS, blood will be obtained/analyzed during Cycle 1 of Part 1, and during additional cycles in Part 1 and/or Part 2 as needed, to measure BVD-523 and selected metabolite concentration levels.

Multiple pharmacodynamics biomarkers will be used to measure response to drug treatment, including evaluation of pRSK and total RSK. Additional biomarkers, including peripheral blood mononuclear cells (PBMCs), and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state. Leukemic cell genotyping by DNA analysis will be performed to identify somatic alterations, relying on either available archived or freshly collected samples. Blood and/or bone marrow aspirate will be collected to determine *ex vivo* BVD-523 sensitivity on leukemic cells prior to therapy on Day 1 and Day 22.

All patients will be screened and eligibility determined prior to enrollment and start of study treatment.

5.1 STUDY PATIENT NUMBER

In Part 1, up to approximately 20 patients are expected to be enrolled.

In Part 2 of the study, up to approximately 40 patients with measurable disease will be enrolled:

- Group 1: patients with RAS mutant positive AML or MDS; n (evaluable) ≤ 20
- Group 2: patients with RAS mutant negative AML or MDS; n (evaluable ≤ 20

5.2 DESCRIPTION OF STUDY VISITS FOR PART 1

Procedures performed in the first cycle are specified in Table 6.3 (Part 1: Schedule of Assessments and Procedures). Patients receiving multiple cycles of treatment will not have blood drawn for PK and PD measurements after Cycle 1 (Day 1 and Day 22) unless additional PK and PD data are deemed necessary after initial analysis.

5.2.1 Visit 1 (Day -28 to -1); Screening

The following procedures will be performed at Visit 1 (Screening):

- Obtain written informed consent (before start of any study-related procedures that are not considered Standard of Care) including optional consents for additional future analyses (Note: informed consent may be obtained up to -28 days to allow flexibility in scheduling of the screening procedures).

- Evaluate all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Review medical history including all previous cancer treatments.
- Record prior and concomitant medications including start/stop dates, indication, dose and frequency taken within 30 days of Cycle 1, Day 1.
- Record demographic data including date of birth, age, gender, race, and smoking status. Where full DOB is collected, initials will not be used.
- Measure and record height in cm and weight in kg.
- Perform and record physical examination.
- Assess and record performance status (ECOG) within 72 hours before start of treatment.
- Record vital signs. Measure body temperature, systolic / diastolic blood pressure (BP) and pulse rate.
- Collect blood for a serum pregnancy test for female patients who are not postmenopausal or surgically sterile. If positive, repeat and confirm results prior to Visit 2. A second positive test will result in exclusion of the patient from the study.
- Assess and record current disease status within 28 days.
- Bone marrow aspirate and/or biopsy within 28 days of Visit 1. Peripheral, Geimsa and Iron stained slides will be collected with each bone marrow aspirate or biopsy. Bone marrow aspirate and/or biopsy slides will not be shipped to a third party. As such, the site may utilize BM aspirates performed in clinical practice as SOC, as long as they are collected within the screening window (-28 days).
- Bone marrow cytogenetics in accordance with local pathology requirements. (Cytogenetics would preferably include at least 20 clones).
- Collect blood samples for blood chemistries, hematology and calculated creatinine clearance within 72 hours before start of treatment, analyze, review and report any clinically significant abnormalities to Medical Monitor before dosing.
- Perform and record ophthalmology examination.
- Obtain a 12-lead electrocardiogram (ECG), and echocardiogram (ECHO) or multi-gated acquisition (MUGA) for left ventricular ejection fraction (LVEF).
- Collect urine samples for urinalysis within 72 hours before start of treatment.
- For patients enrolled in Part 2 of this study, bone marrow sample and/or peripheral blood samples will also be required to obtain necessary RAS genetic information.
- Complete Screening/Enrollment Form and submit to Medical Monitor for review prior to treatment of patient.

5.2.2 Visit 2 (Day 1 ± 0); Baseline/Drug Dispensing/Initiation of Treatment

The following procedures will be performed at Visit 2 (Baseline):

- Review Screening/Enrollment Form to confirm consent to enroll obtained from Medical Monitor or Sponsor.
- Review all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Review medical history for any changes since Screening Visit.

- Record medications including start/stop dates, indication, dose and frequency for any changes since Screening Visit.
- Perform and record physical examination.
- Measure and record weight in kg.
- Assess and record performance status (ECOG) if not done during Screening Visit within 72 hours of start of treatment.
- Record vital signs (body temperature, systolic / diastolic BP and pulse rate).
- ONLY if the screening pregnancy test was performed more than 1 day previously, collect blood for a repeat serum pregnancy test for female patients who are not postmenopausal or surgically sterile.
- Collect pre-dose blood samples for pharmacokinetic (PK), pharmacodynamic (PD), and PBMC analyses.
- Collect pre-dose blood samples for blood chemistries, hematology and creatinine clearance if not done during Screening Visit within 72 hours of start of treatment.
- Collect pre-dose urine samples for urinalysis.
- Administer first dose of BVD-523.
- Collect post-dose blood samples for pharmacokinetic (PK), pharmacodynamic (PD), and PBMC analyses.
- Assess and record adverse events (AEs).
- Dispense study drug and instruct patients how to take study drug, daily every 12 hours ± 2 hours with at least 8 ounces of water on an empty stomach, i.e., fasting (30-60 minutes before food or 2 hours after food).
- Inform patients of the potential photosensitizing effects of BVD-523 and instruct them to avoid sunlight and wear protective clothes, sunglasses, and apply sunblock when outside, including when driving a car.

5.2.3 Visit 3 (Day 8 ± 1)

The following procedures will be performed at Visit 3 (Day 8):

- Review medical history.
- Record concomitant medications including start/stop dates, indication, dose and frequency taken after Visit 2.
- Perform and record targeted physical examination as appropriate.
- Assess and record performance status (ECOG).
- Record vital signs. Measure body temperature, systolic / diastolic BP and pulse rate.
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Dispense drug supply for self-dosing, and remind patients of dosing instructions.
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Obtain a 12-lead ECG.
- Assess and record AEs.

5.2.4 Visit 4 (Day 15 ± 1)

The following procedures will be performed at Visit 4 (Day 15):

- Review medical history.
- Record medications including start/stop dates, indication, dose and frequency taken after Visit 3.
- Perform and record targeted physical examination as appropriate.
- Assess and record performance status (ECOG).
- Record vital signs (body temperature, systolic / diastolic BP and pulse rate).
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Dispense drug supply for self-dosing.
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Assess and record AEs.

5.2.5 Visit 5 (Day 22 ± 1 of Cycle 1, first day of Cycle 2)

The following procedures will be performed at Visit 5 (Day 22 of Cycle 1, Day 1 of Cycle 2):

- Review medical history including all cancer treatments received since previous visit.
- Record medications including start/stop dates, indication, dose and frequency taken after Visit 4.
- Perform and record targeted physical examination as appropriate.
- Measure and record weight in kg.
- Assess and record performance status (ECOG).
- Bone marrow aspirate and/or biopsy. Peripheral, Geimsa and Iron stained slides will be collected with each bone marrow aspirate or biopsy. Following Cycles 1 and 2, Day 22 bone marrow aspirates will be collected only every other cycle, i.e., Cycle 4, etc.
- Bone marrow cytogenetics in accordance with local pathology requirements. (Cytogenetics would preferably include at least 20 clones).
- Record vital signs. Measure body temperature, systolic / diastolic BP and pulse rate.
- Collect pre-dose blood samples for pharmacokinetic (PK), pharmacodynamic (PD), and PBMC analyses.
    - These assessments should be collected when the patient reaches steady state. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patients are not at steady state, these assessments will be rescheduled and completed at the next visit in which steady state is achieved.
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test is positive, collect blood for a serum pregnancy test. If

serum pregnancy test is positive, withdraw patient from study and contact Medical Monitor.

- Administer BVD-523 and dispense drug supply for self-dosing for Cycle, if appropriate, and remind patient of dosing instructions.
- Collect post-dose blood samples for pharmacokinetic (PK), pharmacodynamic (PD), and PBMC analyses.
  - These assessments should be collected when the patient reaches steady state. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patients are not at steady state, these assessments will be rescheduled and completed at the next visit in which steady state is achieved.
- Assess and record disease status (every 2 cycles).
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Assess and record AEs.

5.2.6 Treatment Discontinuation Visit

At the time of study drug discontinuation, the Treatment Discontinuation Visit should be completed for all patients as soon as possible after the last dose of study drug, and every effort should be made to perform the procedures required.

Patients will return to the clinic or will be contacted for a safety follow-up assessment 30 days ± 3 days after the last dose of study drug was taken; or earlier if subsequent therapy for AML or MDS is initiated prior to 30 days ± 3 days. Only information about AEs and SAEs will be collected at this visit.

The following procedures will be performed at Treatment Discontinuation Visit:

- Review medical history
- Record medications including start/stop dates, indication, dose and frequency.
- Perform and record physical examination.
- Assess and performance status (ECOG).
- Record vital signs. Measure body temperature, systolic / diastolic BP and pulse rate.
- Perform and record ophthalmology examination.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test is positive, collect blood for a serum pregnancy test.
- Assess and record disease status.
- Bone marrow aspirate and/or biopsy. Peripheral, Geimsa and Iron stained slides will be collected with each bone marrow aspirate or biopsy. Collection not needed if termination is due to progression.
- Bone marrow cytogenetics in accordance with local pathology requirements. (Cytogenetics would preferably include at least 20 clones). Collection not needed if termination is due to progression. Collect blood samples for blood chemistries, hematology and creatinine clearance.

- Collect urine samples for urinalysis.
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.

5.2.7 Unscheduled Visits

Additional visits can be performed as appropriate and at the discretion of the investigator.

5.3 STUDY VISITS FOR PART 1 CYCLE 2

Cycle 2 visits and procedures are similar to Cycle 1, although no PK/PD measurements will be made unless specifically requested by Investigator. Refer to Table 6.3 for Cycle 2 assessments and procedures. Bone Marrow aspirates will be obtained at Cycle 1, Day 22 and every 2 cycles thereafter.

5.4 DESCRIPTION OF STUDY VISIT FOR PART 1 CYCLE 3 AND EACH SUBSEQUENT CYCLE OF PART 1

Cycle 3 and subsequent cycles have one scheduled visit per cycle. No PK/PD measurements will be made unless specifically requested by Investigator. Refer to Table 6.3 for Cycle 3 assessments and procedures.

5.4.1 Cycle 3 and Subsequent Cycles Visit (Day 1 ± 1 of each cycle)

The following procedures will be performed at Cycle 3 and Subsequent Cycles Visit:

- Review medical history
- Record medications including start/stop dates, indication, dose and frequency taken since previous visit.
- Perform and record targeted physical examination as appropriate.
- Assess and record performance status (ECOG).
- Measure weight in kg.
- Record vital signs. Measure body temperature, systolic / diastolic BP and pulse rate.
- Perform ECG if appropriate (Patients with a normal ECG during Cycle 1 need not have repeat ECGs during subsequent cycles).
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Perform urine pregnancy test for female patients who are not postmenopausal or surgically sterile. If urine test positive, test, collect blood for a serum pregnancy test.
- Assess and record disease status (every 2 cycles).
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Bone marrow aspirate and/or biopsy. Peripheral, Geimsa and Iron stained slides will be collected with each bone marrow aspirate or biopsy. Following Cycles 1 and 2, Day 22 bone marrow aspirates will be collected only every other cycle, i.e., Cycles 4, 6, etc.

- Bone marrow cytogenetics in accordance with local pathology requirements. (Cytogenetics would preferably include at least 20 clones).
- Dispense BVD-523 for 21 days ±4 days of Cycle. Extra doses may be dispensed at the Investigator's discretion to insure continuous dosing.

5.5 DESCRIPTION OF STUDY VISITS FOR PART 2

Study procedures for Part 2 will be the same as those for Part 1. If clinical experience gained in Part 1 requires significant deviations in Part 2 from the procedures in Part 1, these changes will be addressed in a protocol amendment.

6 METHODS OF ASSESSMENT AND CRITERIA FOR EVALUATION

All trial data will be recorded on the electronic case report forms (eCRFs) (TEMPO™). Photographs will be taken in the event a patient experiences a rash, and the photos will be uploaded into the eCRF. Blood and biopsy specimens will be sent to a third party laboratory vendor for analysis.

6.1 DEMOGRAPHIC DATA

At Visit 1 (Screening), patient demographic data will be collected. These include date of birth, age, gender, race, ethnicity, AML or MDS subtype and molecular abnormalities (when available).

6.2 MEDICAL HISTORY

At Visit 1 (Screening), a complete medical history will be obtained from each patient. For female patients of child-bearing potential, the date of the last menstrual period will be noted. Smoking history and prior cancer therapy will be recorded. Data will be reviewed at Visit 2 (Baseline) and updated at subsequent visits.

6.3 CONCOMITANT MEDICATIONS

A detailed history of medications, including prior anti-cancer therapies, and procedures will be documented for each patient at Visit 1 (Screening) and Visit 2 (Baseline). Concomitant medications (especially changes in medication, including any anti-cancer therapies) will be documented for each patient at each scheduled visit. Necessary supportive care such as anti-emetics and anti-diarrheals, etc., will be allowed. Medications which are known to be strong inhibitors of CYP3A4, CYP2D6, and CYP1A2, or strong inducers of CYP3A4, are not permitted during the study (for list of non-permitted drugs, see Appendix 1).

Hydroxyurea will be allowed for all subjects during Cycle 1 of treatment unless subject does not meet inclusion criterion for hydroxyurea use based on kinetics of leukemia. After Cycle 1, hydroxyurea will not be allowed for any subject on study.

6.4 PHYSICAL EXAMINATION

- Height in centimeters (cm) will be measured at Visit 1 (Screening).
- Body weight in kilogram (kg) will be measured at screening and at the beginning of each cycle.

- Body temperature will be measured at each visit.
- Systolic and diastolic BP and pulse rate will be measured at each visit after the patient has been in a supine position for 5 minutes. Blood pressure should be assessed on the same arm during the study.

Full physical examination evaluations at screening should include general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological examinations. Subsequent targeted physical exams should include body systems as appropriate.

Information about the physical examination must be present in the source documentation at the study site. The result of the physical examination prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions Case Report Form. Clinically relevant findings made after the start of study drug, which meet the definition of an adverse event, must be recorded on the Adverse Event Case Report Form.

6.5 SAFETY ASSESSMENTS

Safety evaluations will be conducted at baseline, on Days 1, 8, 15, 22, 29, 36, 43, and, in patients who continue treatment, every 3 weeks or if clinically indicated thereafter. These evaluations will include a targeted physical examination, electrocardiography in subjects where clinically indicated and clinical laboratory studies. An ophthalmologic assessment will be conducted at baseline, at the end of study and at other visits by an ophthalmologist if clinically indicated.

The following clinical laboratory tests will be performed:

- **Hematology** (blood sample: EDTA) – hemoglobin, hematocrit, white blood cells (WBC) count with differential, red blood cells (RBC) count, and platelet count.
- **Blood Chemistry** (blood sample: serum) – albumin, alkaline phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, blood urea nitrogen (BUN) uric acid, cholesterol and triglycerides (at screening and first day of Cycle 1).
- If the total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
- **Urinalysis** – specific gravity, pH; semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood and a microscopic examination including RBC, WBC and casts will be performed if the dipstick is abnormal.

Blood chemistry will be analyzed at each trial center by a certified laboratory and a report of the laboratory values will be sent to the trial center. The investigator or designee will review the laboratory report within 24 hours (except during clinic holidays, when review will be performed within 72 hours) after receipt of the results and assess the clinical significance of all abnormal values. Results must be reviewed prior to dosing and appropriate action taken for any clinically significant abnormal values. Values will be documented on the laboratory report until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication) or baseline. Any laboratory value that remains abnormal at the end-of-study (EOS) and that is considered clinically significant will be followed according to

accepted medical standards for up to 30 days or until resolution of the abnormality or return to baseline.

Ophthalmologic examinations include best-corrected visual acuity, visual field examination intraocular pressure, external eye examination, and dilated fundoscopy. For additional details refer to study manual. Note: any patient experiencing vision changes must stop taking BVD-523 and have an ophthalmic evaluation. Study drug may be re-started when symptoms resolve.

Toxicity will assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03.

6.6 PHARMACOKINETICS

Please refer to Section 6.9.

6.7 PHARMACODYNAMICS

Multiple biomarkers intended to demonstrate inhibition of the molecular target and mechanism of action will be investigated, including pRSK and total RSK. Additional biomarkers, including PBMCs, and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state.

Leukemic cell genotyping by DNA analysis may be performed to identify somatic alterations, relying on either available stored samples or freshly collected samples. Additional blood and/or bone marrow aspirate samples may also be collected to determine *ex vivo* BVD-523 sensitivity on leukemic cells by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state.

6.8 EFFICACY

All responses will be documented. The following is a summary of the response criteria; the detailed criteria based on the published references will be used for analysis.

MDS – The response criterion for evaluation of MDS is based on the International Working Group (IWG) criteria published in 2006 (2).

Table 6.1 Table 3 from IWG 2006 MDS Response Criteria

Complete Response (CR): the following for 4 weeks		
Peripheral: Marrow:	normal peripheral counts with persistent granulocyte count ≥ 1.0 X 10^9/L, platelet count ≥ 100 X 10^9/L normal bone marrow with persistent marrow blasts ≤ 5%; persistent dysplasia will be noted	
Partial Response (PR): the following for 4 weeks		
Peripheral: Marrow:	normal peripheral counts with granulocyte count ≥ 1.0 X 10^9/L and platelet count ≥ 100 X 10^9/L normal bone marrow with marrow blasts > 5% but were reduced by 50% or more	
Marrow Complete Response (mCR): the following for 4 weeks		
Reduction of bone marrow blasts to ≤ 5% without normalization of peripheral counts		
Hematological Improvement (HI): lasts at least 8 weeks*		
Erythroid Response (HI-E):	*Major Response:*	hemoglobin increase ≥ 1.5 g/dL or RBC transfusion independence
Platelet Response (HI-P):	*Major Response:*	absolute increase of platelet count from <20 to > 20 X 10^9/L and by at least 100%, or if more than 20 X 10^9/L, by an absolute increase of at least 30 X 10^9/L
Neutrophil Response (HI-N):	*Major Response:*	granulocyte increase ≥ 100%, and by an absolute increase ≥ 0.5 X 10^9/L

*Abnormal baseline counts were the averages of at least two measurements over at least one week prior to therapy, not influenced by transfusions.

Reference: (2).

Please note that all other responses are collected as "Less than PR" within the eCRF.

AML – The response criteria for AML will be based on modified recommendation of the International Working Group (IWG) published in 2003 (1). Information regarding transfusion dependence will be noted as a visit assessment and space provided in the eCRF.

Table 6.2 Table 4 from IWG 2003 AML Response Criteria

Response	Peripheral Blood	Bone Marrow
CR	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L, independence from red cell and platelet transfusions over the past week	≤ 5% blasts
CRp	ANC > 1.0 x 10^9/L, Platelets < 100 x 10^9/L, independence from red cell transfusions over the past week	≤ 5% blasts
Cri	ANC < 1.0 x 10^9/L	≤ 5% blasts
PR	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L	Decrease of ≥ 50% in blasts to level of 5% to 25%

ANC = absolute neutrophil count; CR=complete remission; CRp=complete remission with incomplete platelet recovery; Cri=CR with incomplete blood count recovery; PR=partial remission.
Reference (1).

Please note that all other responses are collected as "Less than PR" within the eCRF.

6.9 PHARMACOKINETIC PROCEDURES

6.9.1 Blood Sampling and Processing

Samples for PK analysis of BVD-523 and selected metabolites will be obtained from all patients during their first cycle of treatment (Cycle 1). PK samples may also be obtained from patients at unscheduled times or intervals if deemed scientifically or clinically justified at the Investigator's discretion.

At Visit 2 (Baseline), blood samples will be collected prior to dosing, and then at 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours post-dose after the administration of the first dose of the first cycle. At Day 22 (Visit 5; at steady-state), blood samples will be collected prior to dosing and then, 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours post-dose. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patient is not at steady state at Day 22 (Visit 5), these assessments will be rescheduled and completed at the next visit in which steady state is achieved. Comprehensive information on blood sample acquisition, handling and storage are to be found in the study manual. Sample tube labels should include the patient identification number/protocol code, sample number and visit number and will be detailed in the study laboratory manual.

Samples will be stored at -70°C (refer to study manual) at the study center until shipment under appropriate conditions to the analytical laboratory. The analytical laboratory will measure plasma concentrations of BVD-523 using a validated method.

6.9.2 Pharmacokinetic Endpoints

Blood BVD-523 and selected metabolite concentration levels will be measured at specified time points (see Section 3.5.3).

Table 6.4 lists the various parameters that will be calculated.

Table 6.3 Part 1 and 2: Schedule of Assessments and Procedures

		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21 day cycles, visit on 1st day of cycle	
Visit	**1 Screening**	**2 Baseline**	**3 Tx**	**4 Tx**	**5 Tx**	**6 Tx**	**7 Tx**	**8 -X Tx**	**Final Study Visit/ Early Discontinuation**
Visit Day	-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ± 1	36 ± 1	43 ± 1	
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history[a]	X[a]	X	X	X	X	X	X	X	X
Concurrent medications	X	X	X	X	X	X	X	X	X
Demography	X								
Measure height (cm)	X								
Measure weight (kg)	X	X			X			X	X
Physical examination[*]	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Ophthalmology exam[b]	X								X
Pregnancy test[c,d]	X	X[c]			X[d]			X[d]	X[d]
Study drug dispensed		X	X	X	X	X	X	X	
Study drug administration[e]		X			X				
Pharmacokinetic samples[f,g]		X[f,g]			X[f,g]				
Pharmacodynamic samples[f,g]		X[f,g]			X[f,g]				
PBMC samples[f,g]		X[f,g]			X[f,g]				
Assess current disease status**	X				X			X	X
Bone marrow aspirates and/or biopsy[h]	X[k]				X[k]			X[k]	X[k]
Bone marrow cytogenetics[h]	X[k]				X[k]			X[k]	X[k]
Clinical lab tests[i]	X	X	X	X	X	X	X	X	X

Table 6.3 Part 1 and 2: Schedule of Assessments and Procedures

		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21 day cycles, visit on 1st day of cycle	
Visit	**1 Screening**	**2 Baseline**	**3 Tx**	**4 Tx**	**5 Tx**	**6 Tx**	**7 Tx**	**8 -X Tx**	**Final Study Visit/ Early Discontinuation**
Visit Day	-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ± 1	36 ± 1	43 ± 1	
Electrocardiogram (ECG)[j]	X		X						
Adverse events (AEs)		X	X	X	X	X	X	X	X
Compliance by pill count			X	X	X	X	X	X	X
Obtain unused drug			X	X	X	X	X	X	X
ECHO cardiogram or MUGA	X								

Table footnotes:

[a] Full medical history at screening, review/update of history only at subsequent visits.

[b] Ophthalmological examinations will be performed by an ophthalmologist at screening, at study termination and if clinically indicated.

[c] ONLY if the screening serum pregnancy test was performed more than 1 day previously.

[d] After screening and baseline, urine pregnancy test which if positive, confirm with serum test.

[e] Study drug to be taken twice daily, first dose in clinic on days when PK sampling occurs i.e., Cycle 1 on Visit 2 (Day 1) and Visit 5 (Day 22), remaining doses on all other days to be self-administered by patient.

[f] PK blood samples will be collected prior to first morning dose and at 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 12 ±2 hours post-dose. Pharmacodynamic and PBMC blood samples will be collected prior to first morning dose and at 4 hours post-dose.

[g] Pharmacodynamic, PK, and PBMC blood samples are required at baseline where feasible. Additional biomarkers and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state. Leukemic cell genotyping by DNA analysis may be performed to identify somatic alterations, relying on either available stored samples or freshly collected samples.

[h] Bone marrow aspirate and/or biopsy. Peripheral, Geimsa and Iron stained slides to be provided with each bone marrow aspirate or biopsy. Bone marrow cytogenetics (cytogenetics should include at least 20 clones). Bone marrow aspirates may be used to evaluate biomarkers of drug response.

[i] Chemistry (to include calcium and inorganic phosphorus), hematology and urinalysis. After Cycle 2, clinical chemistry (to include calcium and inorganic phosphorus), hematology and urinalysis may be performed once per cycle or more frequently at the investigator's discretion.

[j] Patients with a normal ECG in Cycle 1 need not have repeat ECGs in subsequent cycles. Patients should be supine for 5 minutes prior to the ECG.

[k] Bone marrow aspirates will be obtained at Screening, Cycle 1-Day 22, and every other cycle thereafter. At treatment discontinuation visit, bone marrow aspirates will not be obtained if termination is due to disease progression.

* Physical examinations should be symptom driven after the Screening Visit.

** Assessments of current disease status will be obtained at Screening, Cycle 1–Day 22, and every other cycle thereafter.

Table 6.4 Pharmacokinetic Parameters to be Estimated after Dose 1 and at Steady State

C_{max}	Peak plasma concentration determined manually by visual inspection of plasma concentration vs. time figures on the untransformed (linear) scale of measurement
t_{max}	Time to reach the peak plasma concentration determined manually by visual inspection of plasma concentration vs. time figures on the untransformed (linear) scale of measurement
AUC_{0-12}	Area under the plasma concentration-time curve from 0 to 12 hours post dosing, calculated by linear/log trapezoidal method
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to time of last observation after dosing calculated by linear/log trapezoidal method
λ_z	Elimination rate constant, determined by linear regression of at least 3 points on the terminal phase of the log-linear plasma concentration- time curve. The correlation coefficient (r^2) for the goodness of the fit of the regression line through the data points has to be 0.85 or higher, for the value to be considered reliable. If the WinNonlin data points are not on the linear portion of the terminal slope, the data points will be selected manually prior to calculation of lambda z
$t_{1/2}$	Terminal half-life, defined as 0.693 divided by lambda z

7 DISCONTINUATION CRITERIA

7.1 EARLY DISCONTINUATION OF THE STUDY

It is agreed that for reasonable cause, either the Investigator or the Sponsor may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If discontinuation is by the investigator, notice is to be submitted to BioMed Valley Discoveries, Inc. If discontinuation is by the Sponsor, notice will be provided to each investigator.

If a severe local reaction or drug-related SAE occurs at any time during the study, the Safety Monitoring Committee will review the case immediately.

The study will be immediately suspended and no additional BVD-523 doses will be administered pending review and discussion of all appropriate study data by the SMC if one or more patients at any dose level develop any of the following adverse events deemed to be possibly, probably or definitely related to BVD-523 by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)

The study will not be restarted until all parties have agreed to the course of action to be taken and the Institutional Review Board/Ethic Committee (IRB/EC) (s) has/have been notified.

7.2 DISCONTINUATION OF INDIVIDUAL PATIENTS

Patients are to be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Disease progression (at the discretion of the PI)
- Unacceptable toxicity
- Changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the PI
- At least 3 interruptions of BVD-523 intake of > 7 days each, or 8 consecutive days
- Patient becomes pregnant (withdrawal is required)
- Patient is lost to follow-up

Patients will also to be withdrawn at any time if the Investigator concludes that it would be in the patient’s best interest for any reason. Protocol violations do not lead to patient withdrawal unless they constitute a significant risk to the patient’s safety.

Patients can voluntarily withdraw from the trial for any reason at any time. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, became lost to follow up for any reason, or if any of the following occurs:

- Discovery of patient ineligibility
- Significant errors in treatment compliance of at least three interruptions of 7 days each, any treatment interruption of ≥8 consecutive days, or incomplete dosing for greater than 7 days
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk.

In Part 1 of the study, patients who withdraw at any time due to unrelated AEs preceding the last visit of Cycle 1 (Day 22) will constitute an early discontinuation and must be replaced in order to ensure proper data accrual for dose escalation decisions. A patient who experiences a DLT in Cycle 1 and withdraws before Day 22 either because of the toxicity or otherwise, will nonetheless have that DLT counted in the assessment of potential cohort expansion and/or dose escalation (Table 3.2).

In Part 2 of the study, patients who withdraw at any time preceding the last visit of Cycle 2 (Day 43) will constitute an early discontinuation and will not be replaced and will be evaluated in the Intent to Treat analysis. If patients withdraw due to progressive disease or AEs, replacement of such patients potentially introduces bias into the study. If a patient withdraws for other reasons, replacement of the patient will be decided by the Safety Monitoring Committee.

The investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the eCRF.

8 TREATMENT

The safety and PK of BVD-523 will be tested in sequentially increasing doses starting at 300 mg twice daily, initially in patient cohorts of 3 patients (for tabular summary, see Table 3.2). Dose escalations of BVD-523 will occur in 100% increments in cohorts until one patient experiences a study related ≥ Grade 2 toxicity (excluding alopecia or diarrhea), after which dose increases will be ≤ 50%. If one patient in a 3 patient cohort experiences a DLT as defined in Table 3.2, up to 3 additional patients will be treated at this dose level. If more than one DLT occurs in ≤ 6 patients, this dose level will be defined as the non-tolerated dose and dose escalation will be stopped.

Doses will not be escalated unless the patient(s) receiving the highest current dose have been observed for at least 3 weeks and dose-limiting side effects have been reported in less than 2 of 6 patients assigned to a given dose. Before each escalation, Clinical Investigators will be consulted to ensure that all involved agree with the escalation decision. Once the RP2D has been identified, up to 40 additional patients with pre-defined genetic types will be treated at this dose in Part 2.

Patients experiencing DLT or unacceptable toxicity will have their treatment interrupted until the toxicity returns to ≤ Grade 1 or pre-treatment baseline (whichever is more severe). Resumption of BVD-523 treatment may then be at the next lower dose level where the safety profile has previously been established or between the dose level yielding unacceptable toxicity and the previous dose level, aligning with capsule dose availability.

8.1 DOSING AND ADMINISTRATION OF STUDY MEDICATION

8.1.1 Dispensing Directions

Dispensing instruction will be provided in Pharmacy Instructions in the study manual.

8.1.2 Dosing Information

BVD-523 is to be taken twice daily orally with at least 8 ounces of water for 21 days, at 12-hour ± 2 hour intervals. The study medication should be taken at the same time each day on an empty stomach, i.e., fasting (30-60 minutes before food or 2 hours after food). A patient that is observed to vomit an intact capsule after dosing in the clinic during the PK measurements may receive a substitute dose of drug. However, patients should be instructed NOT to take a substitute capsule if vomiting occurs after self-dosing at home. Missed doses should be skipped and not taken as a double dose at the next dosing timepoint.

Since this is a second-in-human study relatively little human toxicity has thus far been experienced. Therefore, dose modifications for any toxicity seen will be developed as data are accrued. However, patients experiencing DLT or unacceptable toxicity will have their treatment interrupted until the toxicity returns to ≤ Grade 1 or pre-treatment baseline. BVD-523 treatment may then be re-initiated at the next lower dose level where the safety profile has previously been established, or between the dose level yielding unacceptable toxicity and the previous dose level, aligning with capsule dose availability. Such dose adjustments will be done in consultation with the Investigators and Medical Monitor of the study.

8.1.3 Dosing Instructions for the Study Participants

Patients will be instructed to take their study medication twice daily at 12-hour ±2 hour intervals. The study medication should be taken with at least 8 ounces water at the same time each day on an empty stomach (30-60 minutes before food or 2 hours after food).

Drug Storage

Information will be provided in the study manual.

Drug Accountability

The investigator or study staff will verify the integrity of the clinical trial supplies (storage conditions, correct amount received, condition of shipment, kit numbers, etc.) according to Standard Operating Procedures.

The following data will be tracked on the drug accountability log provided by the Sponsor, and recorded in the eCRF:

- Date received
- Lot number
- Date dispensed
- Patient number

Records of study medication (used, lost, destroyed, and returned containers, individual capsules) should be made at each patient visit in the eCRF. Drug accountability and reconciliation will be checked by the site study monitor during site visits and at completion of study treatment.

Unless prohibited by investigational site SOP, used study medication is to be retained until the monitor has verified drug accountability. Once the site monitor has verified drug accountability at the site, any drug remaining in opened dispensing containers will be destroyed. Unused and unopened study medication will be returned to the Sponsor.

8.2 RESCUE MEDICATIONS AND CONCOMITANT TREATMENTS

All medications administered from 30 days prior to the commencement of study treatment (Day 1) through the end of the treatment period (Day 22) will be recorded on the eCRF. Any changes of dosages of medication will also be noted.

8.3 TREATMENT COMPLIANCE

The investigator will dispense the study medication only for use by patients enrolled in the study as described in this protocol. The study medication is not to be used for reasons other than those described in this protocol.

The investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study medication self-administration at Visit 2 (Baseline). Patients will be asked to bring their study medication container with them at each visit and compliance with

protocol-defined study drug intake will be checked by pill count. In case of non-compliance, the patients will be instructed again.

9 ADVERSE EVENT MANAGEMENT

9.1 DEFINITION OF AN ADVERSE EVENT

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE 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 study (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" AEs should be reported on the appropriate page of the eCRF.

9.2 DEFINITION OF A SERIOUS ADVERSE EVENT

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose (including after the ICF is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period (see below). If the malignancy has a fatal outcome during the study or

within the safety reporting period, then the event should be reported using the term "disease progression" with a CTCAE severity of Grade 5.

9.3 RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Recording and reporting of adverse events should be in accordance with the FDA "Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies" of December 2012.

Any AE is to be recorded in the eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single diagnosis.

The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests, e.g., ECG, laboratory assessments, or other study-specified tests (source of AE).

The reporting period begins from the time that the patient provides informed consent through and including 30 calendar days after the last administration of BVD-523. AEs may occur in the specified follow-up period. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the investigational drug is suspected. If the patient begins a new anticancer therapy, the safety reporting period ends at the time the new treatment is started, however, death must always be reported when it occurs during the 30-day reporting period irrespective of intervening treatment.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded. In the event that a rash is noted and reported as an AE, the rash should be documented with photographs as soon as it is reported through resolution. Patients must give consent for photographs to be taken.

9.4 INTENSITY OF ADVERSE EVENTS

The severity of the AE will be graded according to the NCI CTCAE Grading Scale Version 4.03 (see the NCI CTCAE web page at http://ctep.cancer.gov for details). For AEs not covered by NCI CTCAE, the severity will be characterized as "mild", "moderate", or "severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe events interrupt the patient's usual daily activities.

9.5 RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG

The investigator will make a judgment regarding whether or not the AE was related to study drug, as outlined below, and in accordance with FDA guidance of 2012.

Unrelated	The adverse event is unlikely to have been caused by study drug.
Possibly related	It is unclear whether the adverse event may have been caused by study drug.
Related	The adverse event is likely to have been caused by study drug.

9.6 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, related) must be followed until resolution or until stabilization. Any AE of rash should be documented until resolution with photographs.

9.7 POST STUDY ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All unresolved AEs should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study. Prior to the conclusion of the study at the site the investigator should notify the Safety Associate (see Section 9.8) of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. After study conclusion the investigator should notify BioMed Valley Discoveries, Inc., or their designee, Clinipace Worldwide (CPWW), of any death or AE they are aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. BioMed Valley Discoveries, Inc., should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

9.8 REGULATORY ASPECTS OF ADVERSE EVENT REPORTING

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. ALL SAEs must be entered into the eCRF within 24 hours of first knowledge of the event by study personnel. It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report. Entry of an SAE into the eCRF triggers an automatic alert to the CPWW safety team. Timely notification of an event supersedes the requirement to have all information at the time of the initial report.

The following information must be reported on the eCRF SAE report form:

- Protocol number
- Site and/or Investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to Investigative product or not
- Outcome of the event if available

The CPWW Safety Associate will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact:

Safety Associate
Clinipace Worldwide, Inc.
safety@clinipace.com

BioMed Valley Discoveries, Inc., or their designee CPWW, is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA according to 21 CFR 312.32 and the draft guidance (2010). All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Ethics Committee (EC).

9.8.1 Overdose

No information on treatment of overdose of BVD-523 is currently available. In the event of an overdose, the overdose should be reported as an AE and the Medical Monitor should be notified.

9.8.2 Pregnancies

Pregnancy per se is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication. Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

Each pregnancy in a patient or partner of a patient on BVD-523 must be reported to the Sponsor within 24 hours of learning of its occurrence. If a patient becomes pregnant, study drug administration must be discontinued immediately. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Follow-up and documentation must occur even if the patient withdraws from the study or the study is completed.

The avoidance of pregnancy or fathering a child is suggested for 3 months following the discontinuation of BVD-523 therapy. No information is currently available regarding the effects of BVD-523 on fertility, gestation or subsequent child development.

Any pregnancy within 3 months post-study should be reported to the study investigator and to CPWW.

10 STATISTICAL METHODS

10.1 GENERAL CONSIDERATIONS

10.1.1 Statistical and Analytical Plans

A formal detailed statistical analysis plan (SAP) will be created prior to the review of any data.

The purpose of this Phase 1/2 dose escalation study is to determine the maximum tolerated dose (MTD), the dose limiting toxicity (DLT), and the recommended Phase 2 dose (RP2D) of orally administered BVD-523 in patients with AML or MDS. Groups of 3–6 patients will be treated at each dose level until the maximum tolerated dose is reached. All patients meeting the eligibility criteria and receiving at least 1 dose of BVD-523 will be evaluable for safety.

10.1.2 Determination of Sample Size

The sample size for Part 1 of this study was determined by clinical rather than statistical considerations. Approximately 20 patients will be treated in Part 1 of this study (Dose Escalation) to establish dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D).

After the completion of Part 1 of this study, up to 40 additional AML or MDS patients with or without RAS mutations will be treated with the RP2D of BVD-523. The purpose of the second phase of this study is to document that there is some evidence of a response. With 20 subjects in each group, there is an 88% probability of seeing at least one positive response in each group if the true response rate is at least 10%.

The observation of DLTs in more than 33% of patients in any Part 2 cohort with at least 6 patients enrolled at any time during Part 2 will trigger temporary stopping of patient enrollment and revision of the definition of the MTD and RP2D in the specific cohort. Subsequent patients will be treated with a dose lower than the initial RP2D and this dose will be determined in discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor.

Up to 6 study centers are expected to enroll patients for this study.

10.1.3 Blinding and Randomization

This clinical study is open-label, and all patients enrolled will be treated with BVD-523.

10.2 ANALYSIS DATASETS

10.2.1 Population to be Analyzed

The safety population will consist of all patients receiving at least 1 dose of study medication.

10.2.2 Modified Intent-to-treat

The modified intent-to-treat (mITT) population will consist of all patients who have a screening visit/sign the informed consent.

10.2.3 Per Protocol

The per-protocol (PP) population for efficacy evaluations will consist of all patients of the mITT population who completed the study without a major protocol deviation.

10.2.4 Definition of Study Days

In the first treatment cycle, a total of 5 visits are planned for Part 1 of this clinical study. In subsequent Cycles there will be up to 4 visits. Patients in Part 2 of the study will receive a total of up to 5 visits in the first treatment Cycle, and 4 visits in subsequent Cycles. The study visits are defined as summarized in Table 10.1.

Table 10.1 Per Cycle Study Visit Definitions

Visit Description	Study Day
Visit 1: Screening	Day -28 to -1
Visit 2: Baseline / Drug Dispensing / Initiation of Treatment	Day 1 ± 0
Visit 3: Treatment Phase	Day 8 ± 1
Visit 4: Treatment Phase	Day 15 ± 1
Visit 5: Final Visit	Day 22 ± 1

10.3 DATA PRESENTATION

10.3.1 Demographic

Demographic characteristics of patients will be summarized in appropriate tables and analyzed with descriptive statistics.

The following characteristics will be summarized in the mITT, PP, and safety population:

- Age
- Gender
- Race
- Ethnicity
- AML or MDS including relapsed or refractory status
- Bone marrow cytogenetics
- RAS

10.3.2 Baseline Characteristics

Baseline characteristics will be summarized in appropriate tables and with descriptive statistics.

The following characteristics will be summarized in the mITT, PP, and safety population:

- Body weight
- Height
- ECOG performance status

- Previous chemotherapy
- Previous immunotherapy

10.3.3 Medical History and Physical Examination

Descriptive statistics will be generated to summarize data. For continuous variables, descriptive statistics may include the number of patients, mean, standard deviation, median, minimum, maximum; frequencies and percentages may be displayed for categorical data.

10.3.4 Concomitant Medications or Treatments

The number and percentage of patients taking concomitant medication will be summarized. All data will be recorded as follows:

- Prior use ended before first day of trial medication
- Concomitant use on or after first day of trial medication (initiation date, stop date)

10.3.5 Primary Endpoints

MTD – See Section 3.1.4.1.

RP2D – See Section 3.1.4.3.

Measurement of preliminary clinical effects on AML or MDS response.

10.3.6 Secondary Endpoints

Pharmacokinetic profile of BVD-523 and selected metabolites.

Determination of PFS and DOR of patients achieving CR/CRp.

No formal efficacy analysis will be conducted.

10.3.7 Pharmacokinetic Data

Blood BVD-523 and Selected Metabolite Concentration Levels

Systemic BVD-523 exposure as measured in blood samples will be summarized per time point by means of descriptive statistics. Measured concentrations will be presented by a by-patient listing, sorted by site, patient identifier and dose.

10.3.8 Safety Data

All safety summaries will be provided for the Safety population.

Summaries for safety variables (physical examinations, vital signs, clinical laboratory analyses) will be given. All safety variables will be presented in by-patient listings, sorted by site and patient identifier.

10.3.9 Adverse Events (AE)

Adverse events will be coded using the MedDRA coding dictionary. A listing of all events, with seriousness, severity, relationship, sequelae and begin and end times will be provided. Narratives for any serious adverse events will be provided.

Deaths, serious adverse events (SAEs), and AEs leading to discontinuation of trial medication will be summarized by primary system organ class (SOC) and preferred terms. Listings will be provided.

10.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, the IRB/EC and the Health Authorities.

11 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

11.1 DECLARATION OF HELSINKI

The Investigator will ensure that this Study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

11.2 GOOD CLINICAL PRACTICE

The Study will be conducted according to the study protocol and to Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Conference on Harmonization (ICH) for Good Clinical Practice in clinical studies.

11.3 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

Before implementing this study, the protocol, the proposed patient informed consent forms and other information for the patients, must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The IRB/EC written, signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date and version number), and of the patient informed consent form (date, version).

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, the IRB/EC and the Health Authorities.

11.4 REGULATORY AUTHORITY APPROVAL

Before implementing this study, the protocol must be approved by the relevant regulatory authority.

11.5 PRE-STUDY DOCUMENTATION REQUIREMENTS

To be provided.

11.6 INFORMED CONSENT

The investigator must fully inform the patient of all pertinent aspects of the trial including the written information approved/favorably assessed by the IRB/EC.

Prior to the start of the pre-study examination, the written informed consent form must be signed and personally dated by the patient and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to each patient and 1 copy must be retained in the investigator's study records.

Additionally, consent will be requested to obtain/retain a blood sample for future analysis as warranted by our rapidly-advancing understanding in this field. Each patient’s Informed Consent document will reflect that samples collected may be used for pharmacogenomic investigations.

11.7 PATIENT CONFIDENTIALITY AND DISCLOSURE

Data on patients collected on eCRFs during the trial will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient participating in the trial is violated. Likewise, the appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

11.8 COLLECTION, MONITORING AND AUDITING OF STUDY DOCUMENTATION, AND DATA STORAGE

Collection of Data and Monitoring Procedures

This study will use a 21 CFR Part 11 compliant electronic data capture system (TEMPO™). An electronic case report form (eCRF) is used for data recording. All data requested on the eCRF must be entered and all missing data must be accounted for.

The data will be checked for completeness and correctness as it is entered by the real-time online checks applied by TEMPO™. Off-line checks will also be run to perform any additional data review required. Discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or his/her designee.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug–dispensing log by the investigator.

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and case report forms with the investigators and their staff. During the study a monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment. The monitor will ensure during on-site visits that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitors during these visits.

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the case report form entries. No information in these records about the identity of the patients will leave the study center. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

Auditing Procedure

In addition to the routine monitoring procedures the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of Good Clinical Practice.

The investigator agrees that representatives of the Sponsor and Regulatory Authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

Retention of Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep a copy of the signed informed consent form. All information on case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the case report forms, which will be documented as being the source data.

11.9 DISCLOSURE OF INFORMATION

All information provided to the investigator by BioMed Valley Discoveries, Inc., or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to BioMed Valley Discoveries, Inc., or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

11.10 DISCONTINUATION OF THE STUDY

It is agreed that, for reasonable cause, either the investigator or BioMed Valley Discoveries, Inc., may terminate the investigator’s participation in this study after submission of a written notice. BioMed Valley Discoveries, Inc., may terminate the study at any time upon immediate notice for any reason, including the Sponsor’s belief that discontinuation of the study is necessary for the safety of patients.

11.11 STUDY REPORT, PUBLICATION POLICY AND ARCHIVING OF STUDY DOCUMENTATION

11.11.1 Study Report and Publication Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study will be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions and the Sponsor.

11.11.2 Study Documents

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep a copy of the signed informed consent form. All information on the e-case report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the e-case report forms, which will be documented as being the source data.

11.11.3 Archiving of Documents

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/EC approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies (electronic copies on a CDROM)
4. Patients' informed consent forms (with study number and title of trial)
5. FDA form 1572
6. Any other pertinent study document

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Appendix 1 Non-Permitted Concomitant Medications

INHIBITORS CYP3A	INHIBITORS CYP2D6	INHIBITORS CYP1A2
indinavir	bupropion	fluvoxamine
nelfinavir	fluoxetine	ciprofloxacin
lopinavir/ritonavir	paroxetine	enoxacin
clarithromycin	quinidine	
itraconazole		
ketoconazole		
voriconazole		
nefazodone		
saquinavir		
telithromycin		
boceprevir		
conivaptan		
posaconazole		
telaprevir		
mibefradil[1]		
grapefruit juice		

INDUCERS CYP3A
carbamazepine
avasimibe[2]
phenytoin
rifampin
St. John's Wort

[1]Withdrawn from the United States market because of safety reasons
[2]Not a marketed drug

Strong inhibitors: ≥ 5-fold increase in AUC or > 80% decrease in CL
Strong inducers: ≥ 80% decrease in AUC
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit; Table 5 (inhibitors) and Table 6 (inducers), dated 7-28-11; Accessed 10-01-15