

## CLINICAL STUDY PROTOCOL

### PHASE 1 DOSE-ESCALATION, SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF BVD-523 IN PATIENTS WITH ADVANCED MALIGNANCIES

#### BVD-523-01

Drug Development Phase:	Phase 1
Investigational Product:	BVD-523
Indication:	Advanced Malignancies
Sponsor:	BioMed Valley Discoveries, Inc. 4520 Main St. 16 <sup>th</sup> Floor Kansas City, MO 64111
Protocol Version and Date:	Amendment 7, 11 April 2016

**Conduct:** In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

#### CONFIDENTIAL INFORMATION

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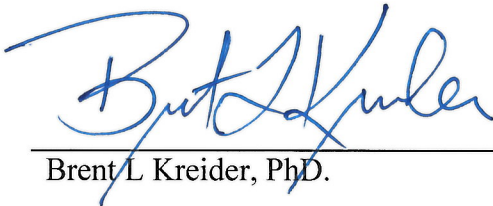
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## PROTOCOL APPROVAL SIGNATURE PAGE

### SPONSOR: BIOMED VALLEY DISCOVERIES, INC

I have read and understand the contents of this clinical protocol amendment 7 for Study No. BVD-523-01 dated 11 April 2016 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



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Brent L Kreider, PhD.

4/13/16

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Date

Chief Operations Officer, BioMed Valley Discoveries, Inc.

## PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol amendment 7 for Study No. BVD-523-01 dated 11 April 2016 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:

Name of Principal Investigator:

<Enter Name and Title>

<Enter Clinic>

<Enter Address>

Phone: <Enter Phone Number>

Fax: <Enter Fax Number>

---

**Signature**

**Date**

## PROTOCOL SYNOPSIS

<b>Sponsor:</b> BioMed Valley Discoveries, Inc.	<b>Investigational Product:</b> BVD-523	<b>Developmental Phase:</b> Phase 1
<b>Title of Study:</b>  Phase 1 Dose-Escalation, Safety, Pharmacokinetic and Pharmacodynamic Study of BVD-523 in Patients with Advanced Malignancies		
<b>Protocol Number:</b>  BVD-523-01		
<b>Indication:</b>  Advanced malignancies		
<b>Objectives:</b>  <u>Primary objective:</u>  To define the safety and tolerability of BVD-523 in patients with advanced malignancies by determining the dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).  <u>Secondary objectives:</u>  To determine the pharmacokinetic profile of BVD-523 and selected metabolites in patients with advanced malignancies.  To investigate any preliminary clinical effects on tumor response assessed by physical or radiological exam (RECIST 1.1).  <u>Exploratory objective(s):</u>  To evaluate pharmacodynamic marker (biomarker) measures.		
<b>Methodology:</b>  Open-label, dose-escalation, multicenter Phase 1 study with dose-escalation phase (Part 1) and cohort expansion phase (Part 2).		

<b>Sponsor:</b> BioMed Valley Discoveries, Inc.	<b>Investigational Product:</b> BVD-523	<b>Developmental Phase:</b> Phase 1
<b>Diagnosis and Criteria for Inclusion:</b>		
Patients eligible for inclusion in this trial have to fulfill <u>all</u> of the following criteria:		
<ol style="list-style-type: none"><li>1. Provide signed and dated informed consent prior to initiation of any study-related procedures that are not considered standard of care (SOC).</li><li>2. Male or female patients aged <math>\geq 18</math> years.</li><li>3. Patients with metastatic or advanced-stage malignant tumor, confirmed histologically, for whom no therapy exists that would be curative.</li><li>4. ECOG performance status of 0 (fully active, able to carry out all pre-disease activities without restriction) or 1 (unable to perform physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), measured within 72 hours before the start of treatment.</li><li>5. Predicted life expectancy of <math>\geq 3</math> months.</li><li>6. Adequate renal function [creatinine <math>\leq 1.5</math> times ULN (upper limit of normal)] or GFR of <math>\geq 50</math> mL/min.</li><li>7. Adequate hepatic function [total bilirubin <math>\leq 1.5</math> times ULN; AST (aspartate transaminase) and ALT (alanine transaminase) <math>\leq 3</math> times ULN or <math>\leq 5</math> times ULN if due to liver involvement by tumor.</li><li>8. Adequate bone marrow function (hemoglobin <math>\geq 9.0</math> g/dL; platelets <math>\geq 100 \times 10^9</math> cells/L; absolute neutrophil count <math>\geq 1.5 \times 10^9</math> cells/L).</li><li>9. Adequate cardiac function, <math>\geq</math> institutional lower limit of normal e.g., left ventricular ejection fraction (LVEF) of <math>&gt; 50\%</math> as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); corrected QT interval (QTc) <math>&lt; 470</math> ms.</li><li>10. Contraception:<ul style="list-style-type: none"><li>• For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (no menstrual cycle for at least 12 consecutive months), or compliant with a medically approved contraceptive regimen during and for 3 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen.</li><li>• For men: Must be surgically sterile, or compliant with a medically approved contraceptive regimen during and for 3 months after the treatment period.</li></ul></li><li>11. Willing and able to participate in the trial and comply with all trial requirements.</li><li>12. For Part 2 of the Study ONLY:<ul style="list-style-type: none"><li>• Patient must be diagnosed with specific tumor types and histologies.</li><li>• Patient must bear tumors that harbor specific classes of genetic mutations.</li><li>• Patients must have measurable disease by RECIST 1.1.</li></ul></li></ol>		

<b>Sponsor:</b> BioMed Valley Discoveries, Inc.	<b>Investigational Product:</b> BVD-523	<b>Developmental Phase:</b> Phase 1
<p><b>Criteria for Exclusion:</b></p> <p>Patients who fulfill <u>one or more</u> of the following criteria will not be eligible for inclusion in this trial:</p> <ol style="list-style-type: none"><li>1. 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.</li><li>2. Uncontrolled or severe intercurrent medical condition.</li><li>3. Known uncontrolled brain metastases. Stable brain metastases either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change in the previous 4 weeks, can be allowed.</li><li>4. Any cancer-directed therapy (chemotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives, (whichever is shorter). Patients previously treated with radiotherapy must have recovered from the acute toxicities associated with such treatment.</li><li>5. Major surgery within 4 weeks prior to first dose.</li><li>6. Any use of an investigational drug 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, unless a dose escalation of BVD-523. In addition, any drug-related toxicity except alopecia should have recovered to Grade 1 or less.</li><li>7. Pregnant or breast-feeding women.</li><li>8. Any evidence of serious active infections.</li><li>9. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).</li><li>10. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).</li><li>11. Concurrent therapy with any other investigational agent.</li><li>12. 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 <a href="#">Appendix 1</a>).</li><li>13. Concomitant malignancies or previous malignancies with less than 2 years disease-free interval at the time of enrollment (except non-melanoma skin cancer, cervical cancer in situ, prostate cancer with undetectable PSA). Other concurrent malignancies that are indolent and do not require active treatment must be discussed with the medical monitor prior to enrollment.</li></ol>		

<b>Sponsor:</b> BioMed Valley Discoveries, Inc.	<b>Investigational Product:</b> BVD-523	<b>Developmental Phase:</b> Phase 1
<b>Test Product, Dose and Mode of Administration:</b>  Part 1: BVD-523, starting at 10 mg, with escalating dose levels, twice daily for 21 days, oral.  Part 2: BVD-523, recommended Phase 2 dose (RP2D), twice daily for 21 days, oral.		
<b>Concomitant Medications:</b>  Necessary supportive care such as antiemetics, antidiarrheals, etc., will be allowed. Certain other medications such as stable doses of steroids for brain metastases may also be allowed. Drugs that are strong inhibitors of CYP1A2, CYP2D6 and CYP3A4, or strong inducers of CYP3A4, will not be allowed during the study (for list of non-permitted drugs, see <a href="#">Appendix 1</a> ).		
<b>Study Duration:</b>  Part 1: 10 to 18 months, Part 2: 18 to 24 months		
<b>Criteria for Evaluation:</b>  <u>Safety:</u> Vital signs, physical examination, ophthalmology examination, clinical chemistry, hematology, urinalysis, electrocardiograms (ECG), and Holter monitoring.  <u>Efficacy:</u> Tumor measurements (anti-tumor activity as evaluated using RECIST 1.1).  <u>Pharmacokinetics:</u> Blood, urine, and tissue biopsy (as indicated) BVD-523 and selected metabolite concentration levels.  <u>Pharmacodynamics:</u> Evaluation of multiple biomarkers to characterize drug response (pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA). Additional biomarkers may be identified and measured as appropriate. Tumor genotyping by DNA analysis will be performed to identify somatic alterations, relying on either available archived tissue or freshly-collected samples.		

<b>Sponsor:</b> BioMed Valley Discoveries, Inc.	<b>Investigational Product:</b> BVD-523	<b>Developmental Phase:</b> Phase 1
<b>Statistical Methods:</b> <p>The sample size for Part 1 of this study was determined by clinical rather than statistical considerations. Approximately 40 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).</p> <p>The purpose of Part 2 of this first in human research is to document that there is some evidence of a response. Upon completion of Part 1 of this study, up to approximately 105 evaluable patients with certain cancer types and/or characterized genetic alterations will be treated with the RP2D (which may be the same or lower than the MTD). 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 potentially RP2D in the specific cohort. Subsequent patients will be treated with a dose lower than the initial MTD and this dose will be determined in discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor.</p> <p>Enrollment of up to 15 evaluable patients in each cohort provides an 80% probability of seeing at least one positive response if the true response rate is at least 10%. Allowing for a low response rate in these patient cohorts is appropriate based on unmet medical need.</p>		



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## ABBREVIATIONS AND DEFINITION OF TERMS

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
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 <sub>max</sub>	maximum concentration
CMC	carboxymethylcellulose
CRF	case report form
CSR	central serous retinopathy
CT	computed tomography
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
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
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
g	gram
GCP	good clinical practice

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<b>Abbreviation</b>	<b>Definition</b>
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HCl	hydrochloride
HDL	high-density lipoprotein
hERG	human ether-a-go-go related gene
IC <sub>50</sub>	half maximal inhibitory concentration
ICF	informed consent form
IRB	institutional review board
ITT	intent-to-treat
LD	largest diameter
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
LS	least squares
µg	microgram
m <sup>2</sup>	square meters
MAPK	mitogen-activated protein kinase
MEDDRA <sup>®</sup>	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase/extracellular signal-related kinase
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition
NA	not applicable
NOEL	no observed effect level
ng	nanogram
NSCLC	non-small cell lung cancer
PD	progressive disease
PI	principal investigator
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PSA	prostate-specific antigen
PT	prothrombin time

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<b>Abbreviation</b>	<b>Definition</b>
PTT	partial thromboplastin time
q.d.	once daily
QTc	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
SD	standard deviation
SEM	standard error of the mean
SMC	safety monitoring committee
SOC	standard of care
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V <sub>ss</sub>	volume of distribution at steady state
WBC	white blood cell
WO	Washout



## 1 INTRODUCTION

A critical hallmark of cancer is the activation of cell-growth signaling cascades independent of appropriate growth stimuli (Hanahan 2000). 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 MEK and 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 (McCoy 1983). Later, auto-activating mutations in MAPK protein kinase BRAF were identified in over fifty percent of all late stage melanoma patients (Davies 2002). MEK mutations are rarer, occurring at a frequency of 8% in melanomas (Nikolaev 2012); while ERK mutations resulting in tumorigenesis were only recently reported (Deschenes-Simard 2014). Aberrant activation of the MAPK signaling cascade may be present in a large proportion of cancers, and direct MAPK pathway mutations may account for a preponderance of “driver” mutations in specific cancers.

The US Food and Drug Administration has recently approved two selective BRAF inhibitors, vemurafenib and dabrafenib, as monotherapies for patients with  $BRAF^{V600}$ -mutant metastatic melanoma. Though response rates can be as high as 50%, duration of response is often measured in months, not years. The MEK1/2 inhibitor trametinib is also approved as a monotherapy in this setting, but is more commonly used in combination with a BRAF inhibitor. First-line use of trametinib administered in combination with dabrafenib offers an even greater improvement in overall survival compared with vemurafenib monotherapy, without increased overall toxicity (Robert 2015), highlighting the potential usefulness of simultaneously targeting multiple stages of the MAPK signaling pathway. This therapeutic combination was also associated with a lower incidence of MEK inhibitor-associated rash and BRAF inhibitor-induced hyperproliferative skin lesions compared with each single agent alone (Flaherty 2012). Recently, a phase III trial also demonstrated significant improvements in overall survival (25.1 vs. 18.7 months, hazard ratio [HR] 0.71,  $P = 0.0107$ ), progression-free survival (PFS) (11.0 vs. 8.8 months, HR 0.67,  $P = 0.0004$ ), and overall response (69% vs. 53%;  $P = 0.0014$ ) with dabrafenib plus trametinib versus dabrafenib alone in patients with  $BRAF^{V600Lys/Glu}$  mutation-positive melanoma (Long 2015). Similarly, significant improvements in PFS (9.9 vs. 6.2 months, HR 0.51,  $P < 0.001$ ) and the rate of complete response (CR) or partial response (PR) (68% vs. 45%;  $P < 0.001$ ) has been demonstrated with the combination of vemurafenib plus cobimetinib compared with vemurafenib alone (Larkin 2014). Based on these and related findings, the combination of a BRAF inhibitor

plus an MEK inhibitor has since become a standard targeted treatment option for patients with metastatic melanoma containing *BRAF*<sup>V600</sup> mutations.

Though BRAF/MEK-targeted combination therapy has significantly prolonged PFS compared with single-agent therapeutic options, patients still eventually develop resistance and disease progression after ~9 to 11 months (Robert 2015, Flaherty 2012, Long 2015). Several mechanisms of acquired resistance to BRAF inhibition have been previously identified, including the generation of *BRAF* splicing variants, *BRAF* amplification, development of *MEK1* or *NRAS* mutations, and upregulation of bypass pathways (Poulikakos 2011, Corcoran 2010, Nazarian 2010, Shi 2014, Johannessen 2010). Central to these mechanisms of resistance is the resultant reactivation of ERK signaling, which enables the rapid recovery of MAPK pathway signaling and escape of tumor cells from BRAF inhibitor therapy (Paraiso 2010). Furthermore, alterations in the MAPK signaling pathway have also been shown to confer resistance to BRAF/MEK inhibitor combination therapy, including *MEK1* or *MEK2* mutations and *BRAF* amplification (Wagle 2011, Wagle 2014, Ahronian 2015). ERK inhibition alone or in combination may have the potential to overcome or avoid resistance from upstream mutations, as it is the final target of the MAPK signaling pathway.

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 cancer.

## 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 malignancies, especially those known to harbor activating genetic mutations in components of the MAPK pathway such as the BRAF, ERK or MEK kinases, or members of the RAS GTPase family. Given this biological rationale and relevant supportive data, melanoma, lung, colon, and pancreatic cancers are potential indications for future 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. For instance, a common mutation found in chronic myelogenous leukemia produces the BCR-ABL oncogene, and direct inhibition of this gene product using the kinase inhibitor drug imatinib/Gleevec™ (Ren 2005) provides substantial benefit to patients. Similarly, the observation of genetic amplification and/or overexpression of EGFR (Putz 1999), ErbB2 (Hynes 2005) and Flt-3 (Tse 2000) receptor tyrosine kinase genes led to therapeutics that inhibit each in a potent and specific fashion, and likewise offer improvements to standard of care (erlotinib/Tarceva™ [Perez-Soler 2004]; gefitinib/Iressa™ [Herbst 2004]; cetuximab/Erbitux [Graham 2004]). For these and other targeted therapies, clinical benefit is accompanied by a safety profile broadly favorable compared to cytotoxic drugs: this occurs because each therapy spares healthy tissue, but damages cancer tissue where oncogenic mutations and malignant cell processes are confined.

A unique array of oncogenic mutations cluster in the mitogen-activated protein kinase, or MAPK, pathway, a key signal transduction cascade that controls cell-growth signaling in many tissues (Sebolt-Leopold 2004a, Chang 2003, Hilger 2002, Kohno 2003, Smalley 2003). Activating mutations in RAS GTPase family members are found in ~30% of all cancers (Bos 1989), with particularly high incidence in pancreatic (90%) (Almoguera 1988) and colon (50%) cancer (Salhab 1989). Activating somatic missense mutations of BRAF are frequent in melanomas (up to 80%) (Pollock 2002, Gorden 2003), papillary thyroid (36%) (Xu 2003), colon (up to 18%) (Ikenoue 2003), and ovarian (14%) (Hsu 2004) cancers. 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 (Chang 2003, Sebolt-Leopold 2004b). 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 (Wan 2004), or where activating mutations in RAS, BRAF, or MEK genes have occurred.

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, induces tumor regression and improves overall survival in this defined patient population (Flaherty 2010, Sosman 2012, Chapman 2011).

The development of additional therapies that can modulate 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 (Nazarian 2010, Poulidakos 2011, Shi 2012, Hatzivassiliou 2012). 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 (Hatzivassiliou 2012).

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 SAFETY EXPERIENCE (PRE-CLINICAL AND CLINICAL)**

Human experience with BVD-523 is limited to the ongoing BVD-523-01 and BVD-523-02 studies, thus the entire safety profile of BVD-523 is not known at this time.

Prominent treatment-emergent events in the BVD-523 program include effects on skin and the GI system. Summary details for specific toxicities (both observed and potential) are provided below; additional information is presented in the BVD-523 Investigator's Brochure.

##### **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 has been observed in patients treated with BVD-523 in this first-in-man study, with approximately two thirds of patients experiencing rash and/or pruritus 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, antibiotics), and dose reductions/interruptions as needed. One patient (dosed at 900 mg b.i.d.) in BVD-523-01, experienced an event of grade 3 erythema multiforme that was considered related to BVD-523 and that resulted in dose interruption. Similarly, one patient (dosed at 750 mg b.i.d.) in BVD-523-02 experienced an event of grade 3 erythema multiforme that was considered related to BVD-523 and that resulted in the discontinuation of study drug.

### Gastrointestinal Effects

Preclinical toxicity studies of BVD 523 have provided evidence of exposure-related, reversible gastrointestinal toxicities, and nausea, vomiting and diarrhea have been observed at high frequency in both BVD-523-01 and BVD-523-02, in some cases occurring in association with dehydration and elevated creatinine/renal insufficiency. Nausea, vomiting and diarrhea have been managed with BVD-523 dosing interruptions and supportive medications as needed and, in some cases, dose reduction of BVD-523 has been undertaken. Gastrointestinal hemorrhage (both upper and lower) has been reported in the BVD-523 program with the majority of events assessed as unrelated to study agent.

### Hepatic and Renal Effects

Related events of mild, moderate and severe elevated AST and/or ALT have also been observed in the BVD-523 clinical program and have been managed with interruption of study agent followed in some instances by dose reduction. Related events of mild, moderate and severe increased creatinine have also been observed, sometimes in conjunction with vomiting, diarrhea and dehydration. Management has consisted of study agent interruption, re-hydration and, in some instances, dose reduction or discontinuation of study drug.

### 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). Anemia has been noted in the BVD-523 program. One case of possibly related, grade 3, reversible, thrombotic thrombocytopenia purpura was reported in a patient with melanoma while receiving BVD-523 at a dose of 450 mg b.i.d.

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.

#### 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 further minimized by advising that patients minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. In this first-in-man Phase 1 study, a low number of patients treated with BVD-523 have experienced grade 1 and 2 photosensitivities classified as possibly related and related to study drug. 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 this ongoing first-in-man Phase 1 study, patients treated with BVD-523 have experienced visual changes, including dimmed/blurry vision and unspecified vision changes. In addition, one patient (dosed at 900 mg b.i.d.), experienced an event of central serous retinopathy. 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.

#### Cardiac Effects

The balance of preclinical evidence suggests BVD-523 has a low, but observable, potential to cause QT prolongation. Given potentially unique species sensitivity, as well as possibly unknown consequences following chronic dosing, patients dosed with BVD-523 will be monitored for potential QTc prolongation and related cardiotoxicities, including 12 hour Holter monitoring following dosing on days 1 and 15. There has been one event of possibly related, grade 3 heart failure in a patient with melanoma which occurred after having received 10 days of study drug (600 mg b.i.d.).

#### 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 1 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.

#### 1.4.2 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.

#### 1.4.3 Preclinical 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, so BVD-523 is not considered to have a significant genetic toxicology risk.

While BVD-523 modestly inhibits the hERG current ( $IC_{50}$  3.4  $\mu$ M), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10  $\mu$ g/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  $\mu$ M). Thus BVD-523 is considered to have a low potential to cause QT prolongation in patients, but, as stated, the 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% carboxymethylcellulose (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: a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; for up

to 14 days at dose levels up to 100 mg/kg twice daily; and 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 1 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, it 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 phase. 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: swelling in the neck; decreased forelimb strength; multiple clinical pathology findings; enlarged lymph nodes, spleen, and mammary gland. Based on these findings, 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.

BVD-523 has a measured UV absorbance at 320 nm, which means that it can absorb both UV-A and UV-B. BVD-523 may therefore act as a photosensitizing agent 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.



## 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 advanced cancers. 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 1.4.2), and has potential for application alone or in combination with existing cancer chemotherapeutics.

This first-in-human study is being performed to assess the safety and tolerability of BVD-523 given orally, twice daily for 21-day cycles. The pharmacokinetics and pharmacodynamics of BVD-523 will also be explored after the first doses administered on Day 1, at steady state on Day 15, at the end of the first cycle of treatment (Day 22), and as indicated after completion of Cycle 1. Pharmacokinetic, pharmacodynamics, and/or Holter measurements may be suspended pending review of accumulated patient experience.

### 2.1 RATIONALE FOR THE DOSES AND THE DOSING REGIMEN

The dosing regimen combines both accelerated titration and standard cohort dose escalation schemata, which will be used jointly to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of BVD-523 in human patients.

The proposed human Phase 1 starting dose for BVD-523 is derived from 28-day GLP toxicology studies performed in rodent and non-rodent species and calculated as described in [Senderowicz 2010](#). 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<sup>2</sup>.

Consistent with current clinical practice and dosing convenience, the proposed starting dose for the Phase 1 clinical study with BVD-523 in cancer patients is 10 mg twice-daily (20 mg/day).

Since there are no pre-clinical data to suggest that flat dosing will lead to greater inter-patient PK variability, flat milligram dosing without adjustment for body size will be used in this study ([Mathijssen 2007](#)). The effects of weight and body surface area on PK may be studied retrospectively as part of the PK analysis.

### 3 STUDY DESIGN

#### 3.1 STUDY DESIGN OVERVIEW

This is an open-label, multi-center Phase 1 study to assess the safety, pharmacokinetics, and pharmacodynamics of escalating doses of BVD-523 in patients with advanced malignancies. The study will be conducted at up to 15 sites.

##### 3.1.1 Study Objectives

###### 3.1.1.1 Primary Objective

To define the safety and tolerability of BVD-523 in patients with advanced malignancies by determining the dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).

###### 3.1.1.2 Secondary Objectives

- To determine the pharmacokinetic profile of BVD-523 and selected metabolites in patients with advanced malignancies
- To investigate any preliminary clinical effects on tumor response assessed by physical or radiological exam (RECIST 1.1)

###### 3.1.1.3 Exploratory Objectives

- To evaluate pharmacodynamic marker (biomarker) measures

##### 3.1.2 Study Design

This clinical study comprises 2 parts:

- Part 1: Dose-escalation Phase
- Part 2: Cohort Expansion Phase

Part 1 – Dose-escalation Phase: An accelerated dose escalation plan will be used to establish dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). One to 6 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 10 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 toxicities.

Patients with advanced-stage solid tumors only (no hematological malignancies) will be enrolled in the dose-escalation phase of the study. The study will initially be conducted as an accelerated single patient design, followed by a standard 3 + 3 design, informed by the

accrued safety experience throughout the study (see Table 3.2 below). All dose-escalation decisions will be based on Cycle 1 safety data.

In the accelerated single patient phase, 1 patient will be enrolled in a cohort and an evaluation of dose escalation will take place after the patient has completed the 21-day treatment cycle. If the patient exhibits no Grade 2 or greater adverse events, dose escalation in a 100% increment and enrollment will continue with a single patient per cohort. However, when one patient experiences a  $\geq$  Grade 2 toxicity (excluding alopecia or diarrhea), this cohort and subsequent cohorts will be expanded to at least 3 patients each following the classic 3 + 3 design and dose escalation increments will be reduced from 100% to a maximum of 50%, as determined by discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor. Doses will not be escalated unless the patient(s) receiving the highest current dose has been observed for at least 3 weeks.

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 an additional 3 patients to that same cohort i.e., 3 + 3. When more than 1 DLT occurs in  $\leq$  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  $\leq$  1 DLT occurred, may be explored to 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%).

At any time during the study, the Sponsor and Investigators may request that cohorts should be enlarged or that exploration of intermediate doses between 2 planned escalation steps should be explored. Such requests will be discussed with the Sponsor and Medical Monitor, and should be based on all data existing at that time, including 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, once the RP2D is defined, intra-patient dose escalation to the RP2D will be allowed after a patient has completed at least 1 cycle at their assigned dose and only if the patient has experienced no toxicity above Grade 1, upon request by the PI and discussion with the Medical Monitor and the Sponsor.

Part 2 – Cohort-expansion Phase: Additional patients with particular tumor types and/or cancers harboring specific genetics will be recruited for treatment at the Recommended Phase 2 Dose (RP2D). Patients must have measurable disease by RECIST 1.1. 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 (Section 7.2). Treatment cycles will occur consecutively without interruption except when necessary to manage toxicities.

Total enrollment for Part 2 is targeted at approximately 105 evaluable patients. Patients will be enrolled into 1 of 7 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 BRAF mutated cancer, except those with colorectal or non-small cell lung cancers, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15
- Group 2: Patients with BRAF mutated colorectal cancer, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15
- Group 3: Patients with BRAF mutated melanoma who have progressed or are refractory to BRAF and/or MEK inhibitors; n ≤ 15
- Group 4: Patients with NRAS mutated melanoma, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15
- Group 5: Patients with MEK mutated cancer, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15
- Group 6: Patients with BRAF mutated non-small cell lung cancer, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15
- Group 7: Patients with ERK mutated cancer, not previously treated with BRAF and/or MEK inhibitors; n ≤ 15

Initial enrollment targets for each group may be modified to respond to accrued safety, clinical effect, pharmacokinetic, and pharmacodynamic data. The decision to expand enrollment in one or more groups will be made through consultation among the Principal Investigators, the Medical Monitor and the Sponsor.

**Table 3.1. Study Medication Dosing and Pharmacokinetics/Pharmacodynamics Chart**

	Study Days			
	1	8	15	22
BVD-523 Dosing <sup>1</sup>	X	X	X	X
Pharmacokinetics Sampling	X		X	X
Pharmacodynamics Sampling <sup>2</sup>	X		X	

<sup>1</sup> Dosing is twice daily in 21-day cycles until disease progression. Patients may be treated beyond disease progression for additional 21-day cycles at the same dose level at the Investigator’s discretion. However it is particularly important in patients for which FDA approved BRAF and/or MEK inhibitors are indicated that BVD-523 treatment NOT be continued beyond tumor progression. Study medication for a week of dosing will be dispensed at each visit (± 1 day for Cycles 1 and 2, ± 2 days for later cycles). For treatment cycles after Cycle 2, study medication for 3 weeks of dosing will be dispensed. Additional medication may be dispensed to ensure uninterrupted dosing, if needed.

<sup>2</sup> Pharmacodynamic sampling should only be completed in those patients that consent to optional biopsy. Those patients that do not consent to this collection do not need to have pharmacodynamics samples taken.

### 3.1.3 Summary of Dose Escalation

**Table 3.2. Summary of Dose Escalation**

Observed Safety Outcomes	Action
<b>Single Patient Cohorts</b>	
AEs $\leq$ Gr 1	<ul style="list-style-type: none"> <li>Continue testing with single patient cohorts</li> <li>Escalate by 100% to next dose level</li> </ul>
One AE $\geq$ Gr 2 (excluding alopecia or diarrhea)	<ul style="list-style-type: none"> <li>Expand current and subsequent cohorts to <math>\geq</math> 3 patients</li> <li>Escalate by <math>\leq</math> 50% to next dose level</li> </ul>
1 DLT	<ul style="list-style-type: none"> <li>Expand cohort up to 6 patients</li> </ul>
<b>Standard Escalation Cohorts (3–6 patients)</b>	
No DLTs	<ul style="list-style-type: none"> <li>Escalate by <math>\leq</math> 50% to next dose level</li> </ul>
1 DLT in 3 patients	<ul style="list-style-type: none"> <li>Expand cohort up to 6 patients</li> </ul>
1 DLT in 6 patients	<ul style="list-style-type: none"> <li>Escalate by <math>\leq</math> 50% to next dose level</li> </ul>
> 1 DLT in $\leq$ 6 patients	<ul style="list-style-type: none"> <li>Stop dose escalation</li> </ul>

*Note:* DLT (see Section 3.1.4.2) is defined as any BVD-523 related toxicity in the first 21 days of treatment that results in:

- $\geq$  Grade 4 hematologic toxicity for > 1 day
- Grade 3 hematologic toxicity with complications e.g., thrombocytopenia with bleeding
- $\geq$  Grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain and rash (these become DLTs if the AE persists despite adequate treatment), a doubling of AST/ALT in patients with grade 2 ALT/AST at baseline
- A treatment interruption exceeding 5 days (or an interruption exceeding 7 days for rash, despite adequate treatment) in Cycle 1 (or inability to begin Cycle 2 for > 7 days) due to BVD-523-related toxicity.

Each cohort can only begin when the previous cohort has completed treatment to at least the end of Week 3 without fulfilling a criterion that would prevent dose escalation.

Although dose escalation decisions may be taken upon review of the data from Cycle 1, safety data will be collected from all patients continuing treatment and 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  $\leq$  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)

DLT is defined as BVD-523 related toxicity in the first 21 days of treatment that results in:

- $\geq$  Grade 4 hematologic toxicity for > 1 day

- Grade 3 hematologic toxicity with complications e.g., thrombocytopenia with bleeding
- $\geq$  Grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the AE persists despite adequate treatment), a doubling of AST/ALT in patients with grade 2 ALT/AST at baseline
- A treatment interruption exceeding 5 days (or an interruption exceeding 7 days for rash, despite adequate treatment) in Cycle 1 (or inability to begin Cycle 2 for > 7 days) due to BVD-523-related toxicity

#### 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 BVD 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:

1. Prior to starting each new dose level after the initial cohort.
2. To stop the dose escalation if the MTD has been reached.

### 3.4 STOPPING RULES

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

### 3.5 STUDY ENDPOINTS

#### 3.5.1 Primary Endpoint(s)

##### Safety

- Evaluation of the DLTs of BVD-523
- Determination of MTD of BVD-523
- Determination of RP2D of BVD-523
- Evaluation of treatment-related AEs of BVD-523

### 3.5.2 Secondary Endpoint(s)

#### Pharmacokinetics

- Evaluation of pharmacokinetic parameters of BVD-523 and selected metabolites in patients with advanced malignancies.

#### Efficacy

- Preliminary clinical effects on tumor response assessed by physical or radiological exam (RECIST 1.1).

### 3.5.3 Exploratory Endpoint(s)

#### Pharmacodynamics

- Evaluation of multiple biomarkers to characterize response to drug (pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA). Additional biomarkers may be identified and measured as appropriate. Tumor genotyping by DNA analysis will be performed to identify somatic alterations, relying on either available archived tissue or freshly-collected samples.

## 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 Phase 1 study up to 40 patients with advanced solid tumors will be enrolled in Part 1. One to six patients per treatment cohort will be assigned to receive sequentially higher oral doses of BVD-523.

The purpose of Part 2 of this first in human research is to document that there is some evidence of a response. Upon completion of Part 1 of this study, up to approximately 105 evaluable patients with certain cancer types and/or characterized genetics will be assigned to 1 of 7 treatment arms and treated with the RP2D determined in Part 1 (which may be the same or lower than the MTD). 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 potentially RP2D in the specific cohort. Subsequent patients will be treated with a dose lower than the initial MTD and this dose will be determined in discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor.

Enrollment of up to 15 evaluable patients in each cohort provides an 80% probability of seeing at least one positive response if the true response rate is at least 10%. Allowing for a low response rate in these patient cohorts is appropriate based on unmet medical need.

In Part 2 of the study, patients who withdraw at any time preceding the 1<sup>st</sup> protocol-specified tumor measurement evaluation at the end of Cycle 2 (except for study drug-related AE) will be replaced.

### **4.2 RECRUITMENT**

Three to 10 study centers will enroll up to 40 patients for Part 1.

In addition to the sites supporting Part 1 studies, sites may be added (up to 15 total sites) to enroll up to approximately 105 evaluable patients for Part 2 of the study.

### **4.3 INCLUSION CRITERIA**

Patients eligible for inclusion in this trial have to 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. Patients with metastatic or advanced-stage malignant tumor, confirmed histologically, for whom no therapy exists that would be curative.
4. ECOG performance status of 0 (fully active, able to carry out all pre-disease activities without restriction) or 1 (unable to perform physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), measured within 72 hours before the start of treatment.



5. Predicted life expectancy of  $\geq 3$  months.
6. Adequate renal function [creatinine  $\leq 1.5$  times ULN (upper limit of normal)] or GFR of  $\geq 50$  mL/min.
7. Adequate hepatic function [total bilirubin  $\leq 1.5$  times ULN; AST (aspartate transaminase) and ALT (alanine transaminase)  $\leq 3$  times ULN or  $\leq 5$  times ULN if due to liver involvement by tumor].
8. Adequate bone marrow function (hemoglobin  $\geq 9.0$  g/dL; platelets  $\geq 100 \times 10^9$  cells/L; absolute neutrophil count  $\geq 1.5 \times 10^9$  cells/L).
9. Adequate cardiac function,  $\geq$  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 (no menstrual cycle for at least 12 consecutive months), or compliant with a contraceptive regimen 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 medically approved contraceptive regimen 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 of the Study ONLY:
  - Patient must be diagnosed with specific tumor types and histologies (Section 3.1.2).
  - Patient must bear tumors that harbor specific classes of genetic mutations.
  - Patients must have measurable disease by RECIST 1.1.

#### 4.4 EXCLUSION CRITERIA

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

1. 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.
2. Uncontrolled or severe intercurrent medical condition.
3. Known uncontrolled brain metastases. Stable brain metastases either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change in the previous 4 weeks, can be allowed.
4. Any cancer-directed therapy (chemotherapy, hormonal therapy, biologic or immunotherapy, etc.) within 28 days or 5 half-lives, (whichever is shorter). Patients previously treated with radiotherapy must have recovered from the acute toxicities associated with such treatment.
5. Major surgery within 4 weeks prior to first dose.
6. Any use of an investigational drug 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.

7. Pregnant or breast-feeding women.
8. Any evidence of serious active infections.
9. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study (based on the investigator's judgment).
10. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).
11. Concurrent therapy with any other investigational agent.
12. 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](#)).
13. Concomitant malignancies or previous malignancies with less than 2 years disease-free interval at the time of enrollment (except non-melanoma skin cancer, cervical cancer in situ, prostate cancer with undetectable PSA). Other concurrent malignancies that are indolent and do not require active treatment must be discussed with the medical monitor prior to enrollment.

## 5 STUDY PLAN AND PROCEDURES

This clinical study will consist of 2 parts. In Part 1, patients with advanced solid tumors will receive sequentially higher oral doses of BVD-523.

In Part 2, patients will be assigned to 1 of 7 treatment groups based on specific tumor and clinical characteristics and will be treated at the Recommended Phase 2 Dose determined in Part 1.

To characterize the pharmacokinetic properties of BVD-523 in patients, blood, urine, and tissue biopsy (as indicated) samples will be obtained/analyzed during Cycle 1 of Part 1, and during additional cycles in Part 1 and/or Part 2 as indicated.

Multiple pharmacodynamics biomarkers will be used to measure response to drug treatment, including evaluation of pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA. Biomarker samples/measurements will be obtained during Cycle 1 of Part 1, and during additional cycles in Part 1 and/or Part 2 based on accumulated experience (appropriate control samples/measurements will be taken prior to patient receiving their first dose).

Tumor assessments will be made by CT/MRI/Physical Exam prior to dose initiation, at the 1<sup>st</sup> protocol-specified tumor measurement evaluation at the end of Cycle 2 and then every 2-3 cycles, and at End of Treatment.

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 forty patients are expected to be enrolled.

In Part 2 of the study, up to approximately 105 evaluable patients with measurable disease will be enrolled:

- Group 1: Patients with BRAF mutated cancer, except those with colorectal or non-small cell lung cancers, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$
- Group 2: Patients with BRAF mutated colorectal cancer, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$
- Group 3: Patients with BRAF mutated melanoma who have progressed or are refractory to BRAF and/or MEK inhibitors;  $n \leq 15$
- Group 4: Patients with NRAS mutated melanoma, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$
- Group 5: Patients with MEK mutated cancer, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$

- Group 6: Patients with BRAF mutated non-small cell lung cancer, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$
- Group 7: Patients with ERK mutated cancer, not previously treated with BRAF and/or MEK inhibitors;  $n \leq 15$

## 5.2 DESCRIPTION OF STUDY VISITS FOR PART 1

Procedures performed in the first cycle are specified in Table 6.1. Patients receiving multiple cycles of treatment will not have blood drawn for pharmacokinetic and pharmacodynamic measurements after Cycle 1 unless additional pharmacokinetic and pharmacodynamic data are deemed necessary after initial analysis.

### 5.2.1 Visit 1 (Day -14 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 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 (within previous 28 days) and concomitant medications including start/stop dates, indication, dose and frequency.
- Record demographic data including date of birth, age, gender, race, ethnicity and smoking status.
- Measure and record height and weight.
- Perform and record physical examination.
- Assess and record performance status (ECOG) within 7 days 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.
- Assess and record current disease status (computed tomography [CT] or other measurements to be defined). This may be performed within 28 days before start of treatment (Visit 2).
- Collect blood samples for blood chemistries, hematology and creatinine clearance (In all instances throughout the study, when creatinine clearance is calculated, the Cockcroft-Gault formula should be used.) within 7 days 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), ECHO cardiogram or MUGA for LVEF.
- Collect urine samples for urinalysis within 7 days before start of treatment.
- For patients enrolled in Part 2 of the study, a tumor biopsy and blood may be required to obtain tumor genetic information required to confirm eligibility (e.g., BRAF, MEK, RAS, or ERK mutation).
- For patients who have given consent for optional research tests involving the collection of tumor tissue and plasma samples for circulating tumor DNA analysis, collect tumor biopsy and plasma samples prior to first dose of BVD-523.

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

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

Visit 1 (Screening) laboratory assessments (including Chemistry, Hematology and Urinalysis), ECOG and physical exams completed within 7 days prior to the Cycle 1 Day 1 visit do not need to be repeated pre-dose at this visit. Female patients with a negative serum pregnancy test result within 24 hours of the Cycle 1 Day 1 visit may have a urine pregnancy test performed pre-dose on C1D1.

- Review all inclusion and exclusion criteria to ensure that patients meet all inclusion criteria and none of the exclusion criteria.
- Review medical history.
- Record medications including start/stop dates, indication, dose and frequency.
- Perform and record physical examination.
- Assess and record performance status (ECOG).
- 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 urine for a urine pregnancy test for female patients who are not postmenopausal or surgically sterile.
- Attach Holter monitor for QTc assessment.
- Collect pre-dose blood samples for pharmacokinetic and pharmacodynamic analyses
  - In Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue.
- Collect pre-dose urine samples for pharmacokinetic analyses.
- Collect pre-dose blood samples for blood chemistries, hematology and creatinine clearance.
- Collect pre-dose urine samples for urinalysis.
- Administer first dose of BVD-523.
- Collect post-dose blood samples for pharmacokinetic and pharmacodynamic analyses.
  - In Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue.
- Collect post-dose urine samples for pharmacokinetic analyses.
- Perform and record Holter monitoring during pharmacokinetic sampling.

- Assess and record AEs.
- Dispense study drug and instruct patients how to take study drug.
- 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)

- 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.
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Obtain a 12-lead ECG.
- Assess and record AEs.
- Administer BVD-523 and dispense drug supply for self-dosing.

### 5.2.4 Visit 4 (Day 15 ± 1)

- 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).
- Assess and record AEs.
- Record vital signs (body temperature, systolic/diastolic BP and pulse rate).
- Obtain all unused study drug from patient.
- Assess study drug compliance by pill count.
- Collect blood samples for blood chemistries, hematology and creatinine clearance.
- Collect urine samples for urinalysis.
- Attach Holter monitor for QTc assessment.
- Collect pre-dose urine samples for pharmacokinetic analyses.
- Collect pre-dose blood samples for pharmacokinetic and pharmacodynamic analyses.
  - In Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue.
- Administer BVD-523 and dispense drug supply for self-dosing.
- Collect post-dose blood samples for pharmacokinetic and pharmacodynamic analyses.

- In Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue
- Collect post-dose urine samples for pharmacokinetic analyses.
- Perform and record Holter monitoring during pharmacokinetic sampling.
- For patients who have given consent for optional research tests involving the collection of tumor tissue, collect tumor tissue sample (may be collected 1 day before or up to 2 days after the visit).

Note: If the patient has not completed at least 5 days of continuous dosing before the visit, Holter monitoring, pharmacokinetic sampling, pharmacodynamic sampling, and optional research tests (for patients who have given consent) should not be completed. Patients may be asked to complete these assessments at a future study visit.

### 5.2.5 Visit 5 (Day 22 ± 1 of Cycle 1, first day 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.
- Assess and record performance status (ECOG).
- Record vital signs. Measure body temperature, systolic/diastolic BP and pulse rate.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- 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.
- Collect a pre-dose blood sample for pharmacokinetic analyses.
- Administer BVD-523 and dispense drug supply for self-dosing for Cycle 2 if appropriate.
- Assess and record disease status, including safety, pharmacokinetics, and pharmacodynamics.
- Assess and record AEs.
- For patients who have given consent for optional research tests involving the collection of plasma samples for circulating tumor DNA analysis, collect plasma samples.

### 5.2.6 End of Treatment Visit

At the time of study drug discontinuation, the End of Treatment 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 all procedures.

- 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. CT/MRI/Physical Exam for tumor assessment to be performed if the previous CT/MRI scan was conducted more than 21 days earlier.
- 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 30-day Safety Visit

Patients will be asked to return for a visit or contacted by phone for a follow-up assessment at  $30 \pm 3$  days after the last dose of study drug is taken, or earlier if subsequent therapy is initiated before  $30 \pm 3$  days. Information concerning only SAEs and AEs will be collected at this visit.

#### 5.2.8 Unscheduled Visits

Additional visits can be performed as appropriate and at the discretion of the investigator. Testing may include any previously described assessment including timed pharmacokinetics and pharmacodynamics collections.

### 5.3 STUDY VISITS FOR PART 1 CYCLE 2

Cycle 2 visits and procedures are similar to Cycle 1, although no pharmacokinetic/pharmacodynamic measurements will be made unless specifically requested by Investigator. Refer to Table 6.1 for Cycle 2 assessments and procedures.

### 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 pharmacokinetic/pharmacodynamic measurements will be made unless the Visit 4 or Visit 5 measurements were missed due to dosing interruption or unless specifically requested by Investigator. Refer to Table 6.1 for Cycle 3 assessments and procedures.

#### 5.4.1 Cycle 3 and Subsequent Cycles Visit (Day $1 \pm 1$ of each cycle)

- 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 (CT/MRI/Physical Exam every 2-3 cycles and other measurements to be defined).
- Assess and record AEs.
- Obtain all unused study drug from patient.
- Assess study drug compliance by reviewing pill count.
- Dispense BVD-523 with timing and quantity to ensure continuous treatment.
- For patients who have given consent for optional research tests involving the collection of tumor tissue and plasma samples for circulating tumor DNA analysis, tumor biopsy and plasma samples may be collected after disease progression.

## 5.5 DESCRIPTION OF STUDY VISITS FOR PART 2

Study procedures for Part 2 will be the same as those for Part 1 with three exceptions:

- Urine pharmacokinetics will be discontinued at the completion of Part 1, and
- Blood pharmacokinetics, blood pharmacodynamics, and Holter monitoring may be discontinued prior to completion of Part 2 based on accumulated patient experience, and
  - Based on accumulated patient experience, in Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue.
- The 1<sup>st</sup> protocol-specified tumor measurement evaluation will be performed at the end of Cycle 2 and then every 2-3 cycles.

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.

During the Cohort Expansion phase (Part 2) of the study an alternative BVD-523 capsule formulation may be evaluated. The new drug product contains the same investigational drug substance (BVD-523) in the same dosage form and strength as the initial powder-in-capsule drug product; however it also contains standard excipients commonly used in immediate

release solid dosage forms and is therefore not expected to alter the bioavailability of the drug substance.

## **6 METHODS OF ASSESSMENT AND ENDPOINTS**

All trial data will be recorded on the eCRFs (TEMPO™).

### **6.1 DEMOGRAPHIC DATA**

At Visit 1 (Screening), patient demographic data will be collected. These include: year of birth, age, gender, race, ethnicity, tumor type and molecular abnormalities when available or required for Part 2.

### **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 should be noted. Data will be reviewed at Visit 2 (Baseline) and updated at subsequent visits.

### **6.3 CONCOMITANT MEDICATIONS**

Detailed history of medications and procedures will be documented for each patient at Visit 1 (Screening) and Visit 2 (Baseline). Concomitant medications (especially changes in medication) will be documented for each patient at each scheduled visit. 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](#)).

### **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 with the patient in a supine position. 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 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 physical examination, electrocardiography in subjects with a clinically significant abnormal ECG in Cycle 1 (by ECG and Holter monitoring [Holter for  $12 \pm 2$  hours during PK sampling days]), 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. Patients experiencing dermatological AEs considered to be possibly related to BVD-523 should have digital photographs and punch biopsies taken of the affected skin, if they have given formal informed consent. The following clinical laboratory tests will be performed:

- **Hematology:** hemoglobin, hematocrit, white blood cells (WBC) count with differential, red blood cells (RBC) count, erythrocyte sedimentation rate (ESR) and platelet count.
- **Blood Chemistry:** albumin, alkaline phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), lactic dehydrogenase (LDH), sodium and blood urea nitrogen (BUN) uric acid.
  - 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.
  - Cholesterol, HDL, LDL and triglycerides levels will be measured at screening and the first day of each cycle only.
- **Urinalysis:** specific gravity, pH, semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. Abnormal findings by dipstick will trigger a full microscopic examination including RBC, WBC and casts.

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 will review the laboratory reports before dosing and appropriate action taken to address any clinically significant abnormal values. Laboratory parameters for which clinically significant values are noted will be re-measured on the appropriate clinical follow-up arranged by the investigator. Values will be monitored until stabilized, or the laboratory value returns to a clinically acceptable range (regardless of relationship to study medication). 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.

Ophthalmologic examinations include best-corrected visual acuity, visual field examination intraocular pressure, external eye examination, and dilated funduscopy. For additional details refer to study manual).

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

## 6.6 PHARMACOKINETICS

Please refer to Section 6.9.

PK blood and urine samples may be sent to a third party vendor (for submission instructions, see Study Manual).

## 6.7 PHARMACODYNAMICS

Multiple biomarkers intended to demonstrate inhibition of the molecular target, and mechanism of action will be investigated, including pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA. Additional biomarkers and DNA sequence analysis may be identified and measured as appropriate.

In Part 1, pharmacodynamics blood samples will be taken pre-dose and 4 hours ( $\pm$  10 minutes) post-dose. In the event of intra-patient dose escalation, additional pharmacodynamics samples may be obtained at investigator discretion or sponsor request. In Part 2, pharmacodynamics blood samples will be taken according to the Part 1 schedule, but only in those patients consenting to optional research tests involving collection of tumor tissue and blood/plasma samples.

Tumor genotyping by DNA analysis may be performed in patients in Part 1 and Part 2 to identify somatic alterations. Collection of tumor tissue may also be obtained from selected patients within 3 days (1 day before, 2 days after) of the C1D15 visit day. Additional tissue samples for analysis may also be obtained from selected patients after disease progression. Paired tumor tissue and blood samples will be obtained at baseline. Tissue may consist of formalin-preserved samples obtained at previous surgery or new biopsy tissue in patients with accessible tumors.

Tissue and blood samples may be sent to a third party vendor (for submission instructions, see Study Manual).

## 6.8 EFFICACY

Tumor measurements based on physical examination will occur at baseline and on the first day of each treatment cycle. Tumor assessments will be made by CT/MRI/Physical Exam prior to dose initiation, at the 1<sup>st</sup> protocol-specified tumor measurement evaluation at the end of Cycle 2 and then every 2-3 cycles, and at End of Treatment. Imaging will be performed on the abdomen, chest, pelvis and the site of the primary tumor if elsewhere. The same imaging modality used for an individual patient (i.e., CT or MRI) at Screening should be maintained throughout the study. The findings will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The response criteria are defined as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

CT and MRI scans may be submitted to a central third party vendor for review (for submission instructions, see Study Manual).

## 6.9 PHARMACOKINETIC PROCEDURES

### 6.9.1 Blood Sampling and Processing

In Part 1, samples for PK analysis of BVD-523 and selected metabolites will be obtained from all patients during their first cycle of treatment (Cycle 1). In Part 2, samples for PK analysis of BVD-523 and selected metabolites will be obtained from all patients during their first cycle of treatment (Cycle 1) until the sponsor determines sampling will be discontinued based on accumulated patient experience. Additional PK samples may also be obtained in the event of an SAE, AE, or intra-patient dose-change at the Investigator's or sponsor's request.

At Visit 2 (Baseline) blood samples will be collected prior to dosing, and then at 0.5, 1 ( $\pm 5$  minutes), 2, 4, 6, 8 ( $\pm 10$  minutes), and 12 hours ( $\pm 2$  hours) post-dose after the administration of the first dose of the first cycle. At Day 15 (Visit 4; at steady-state) blood samples will be collected prior to dosing and then 0.5, 1 ( $\pm 5$  minutes), 2, 4, 6, 8 ( $\pm 10$  minutes), and 12 hours ( $\pm 2$  hours) post-dose. A single sample will be collected on Day 22 prior to dosing on that day. Comprehensive information on blood sample acquisition, handling and storage are to be found in the Study Manual. Sample tube labels include the patient identification number/protocol code, sample number and visit number.

For storage and shipping instructions refer to Study Manual. The analytical laboratory will measure plasma concentrations of BVD-523 using a validated method.

### 6.9.2 Urine Sampling and Processing

At Visit 2 (Baseline), urine samples will be collected pre-dose. Total urine for the 1–6-hour and 6–12  $\pm 2$ -hour time periods post-dose after the administration of the first dose of the first cycle will also be collected. At Day 15 (Visit 4; at steady-state) urine samples will be collected pre-dose and then post-dose for the 1–6-hour and 6–12  $\pm 2$ -hour time periods.

For storage and shipping instructions refer to the Study Manual. The analytical laboratory will measure urine concentrations of BVD-523 using a validated method.

Urine samples for PK will not be collected during Part 2 of the study.

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

### 6.9.3 Pharmacokinetic Endpoints

Blood, urine, (as indicated) BVD-523 and selected metabolite (blood samples only) concentration levels will be measured at specified timepoints.

Table 6.2 lists the various parameters that will be calculated.

**Table 6.1. 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 1 <sup>st</sup> 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	-14 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 <sup>1</sup>	X <sup>9</sup>	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 <sup>2</sup>	X								X
Pregnancy test <sup>3,4</sup>	X	X <sup>3</sup>			X <sup>4</sup>			X <sup>4</sup>	X <sup>4</sup>
Study drug dispensed		X	X	X	X	X	X	X	
Study drug administration <sup>5</sup>		X	X	X	X	X	X	X	
Pharmacokinetic samples <sup>6,7</sup>		X <sup>7</sup>		X <sup>6</sup>	X <sup>6</sup>				
Pharmacodynamic samples <sup>6,7,8</sup>		X <sup>7</sup>		X <sup>6</sup>					
Tumor measurements <sup>9</sup>	X							X	X
Clinical lab tests <sup>10</sup>	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG) <sup>11</sup>	X		X						
Holter monitoring <sup>12</sup>		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:

\*Note: informed consent may be obtained up to -28 days to allow flexibility in scheduling of the screening procedures.

- <sup>1</sup> Full medical history at screening, review/update of history only at subsequent visits.
- <sup>2</sup> Ophthalmological examinations will be performed by an ophthalmologist at screening, at End of Treatment and if clinically indicated.
- <sup>3</sup> ONLY if the screening serum pregnancy test was performed more than 1 day previously.
- <sup>4</sup> After screening and baseline, urine pregnancy test which if positive, confirm with serum test.
- <sup>5</sup> 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), Visit 4 (Day 15) and morning dose of Cycle 2 on Visit 5, remaining doses on all other days to be self-administered by patient.
- <sup>6</sup> In Part 1 PK and pharmacodynamic blood samples plus PK urine samples will be taken concurrently on Day 1 and Day 15 along with QTc extractions from the Holter monitoring. PK blood samples will be collected prior to first dose and at 0.5 hours, 1 hour (both  $\pm 5$  minutes), 2 hours, 4 hours, 6 hours, 8 hours (all  $\pm 10$  minutes), and 12 hours ( $\pm 2$  hours) post first dose. Blood samples for pharmacodynamic assessment will be collected pre-dose and 4 hours post-dose ( $\pm 10$  minutes). PK urine samples will be collected prior to first dose and for the 1–6-hour and 6–12  $\pm 2$ -hour time periods post first dose on Day 1 and Day 15. On Day 22, PK and pharmacodynamic samples will be collected prior to the first dose of that day. In Part 2, urine PK will not be performed and blood PK, blood pharmacodynamic, and Holter monitoring will be performed until the sponsor determines they will be discontinued based on accumulated patient experience.
- <sup>7</sup> PK and pharmacodynamic blood and urine samples are required, and paired tumor tissue and blood samples are to be obtained at baseline where feasible. Tumor genotyping by DNA analysis may be performed to identify somatic alteration. Additional tissue or plasma DNA samples for analysis may also be obtained from selected patients prior to first dose, at steady-state during treatment, or dose change, and/or after disease progression.
- <sup>8</sup> In Part 2, pharmacodynamic samples only need to be taken if the patient has consented to the optional research tests involving collection of tumor tissue.
- <sup>9</sup> Tumor assessments will be made by CT/MRI/Physical Exam prior to dose initiation if the patient does not have a recent CT/MRI/Physical Exam on record within 28 days before start of treatment (Visit 2), at the 1<sup>st</sup> protocol-specified tumor measurement evaluation at the end of Cycle 2 and then every 2-3 cycles, and at End of Treatment if the previous CT/MRI/Physical Exam was conducted 21 or more days earlier. The same imaging modality used for an individual patient (i.e., CT or MRI) at Screening should be maintained throughout the study.
- <sup>10</sup> 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.
- <sup>11</sup> Patients with a normal ECG in Cycle 1 need not have repeat ECGs in subsequent cycles.
- <sup>12</sup> Holter monitoring for 12 $\pm$ 2 hours during PK sampling.

**Table 6.2. 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
$AUC_{1-12}$	Area under the plasma concentration-time curve from 1 to 12 hours post-dosing, calculated by linear/log trapezoidal method (for use in calculating $CL_r$ )
$AUC_{0-last}$	Area under the plasma concentration-time curve from time 0 to time of last observation after dosing calculated by linear/log trapezoidal method
$\lambda_z$	Terminal phase 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 (ln 2) divided by lambda z
$U_{1-12}$	Amount excreted in urine calculated from Time 1 to 12 hours
$CL_r$	Renal clearance, $U_{1-12}$ divided by $AUC_{1-12}$
$Ae\%$	Percentage of the dose excreted in the urine, $U_{1-12}$ divided by the dose and multiplied by 100.

## 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 by the investigator notice is to be submitted to BioMed Valley Discoveries, Inc., and if 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 administered pending review and discussion of all appropriate study data by the SMC if 1 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 IRB/EC has been notified.

### 7.2 EARLY 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). However it is particularly important in patients for which FDA approved BRAF and/or MEK inhibitors are indicated that BVD-523 treatment NOT be continued beyond tumor progression.
- Unacceptable toxicity
- Changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the PI
- Patient non-compliance as assessed by the investigator
- Patient has a positive serum pregnancy test (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, or became lost to follow up for any reason.

In Part 1 of the study, patients who withdraw at any time 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 Course 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 (see Table 3.2).

In Part 2 of the study, patients who withdraw at any time preceding the 1<sup>st</sup> protocol-specified tumor measurement evaluation at the end of Cycle 2 (except for study drug-related AE) will be replaced.

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 10 mg twice daily, initially in single-patient cohorts (for tabular summary, see Table 3.2). Dose escalations of BVD-523 will occur in 100% increments in single-patient cohorts until one patient experiences a  $\geq$  Grade 2 toxicity (excluding alopecia or diarrhea). This cohort and subsequent cohorts will be expanded to at least 3 patients each and subsequent dose-escalation increments will be reduced from 100% to a maximum of 50%, as determined by discussion with the Clinical Investigators, the Medical Monitor, and the Sponsor. 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  $\leq$  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 tumor types will be treated at this dose.

Patients experiencing DLT or unacceptable toxicity will have their treatment interrupted until the toxicity returns to  $\leq$  Grade 1 or pre-treatment baseline, whichever is more severe. Resumption of BVD-523 treatment may then be at the next lower dose level tested or at a 20–30% dose decrease, aligning with capsule dose availability.

During Part 2 of the study, inpatient dose modifications are allowed, including dose reductions/interruptions as needed and re-escalations up to and including RP2D, at Clinical Investigators' discretion.

### 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 for 21 days, at  $12 \pm 2$ -hour intervals. The study medication should be taken with 8 ounces of water at the same time each day on an empty stomach i.e., fasting (30-60 minutes before food or 2 hours after food). All capsules, if more than one is taken at each dosing time, should be taken within 10 minutes. 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. Patient dosing dates and times will be collected.

Since this is a first-in-human study no human toxicity has yet been experienced and, therefore, dose modifications for any toxicity seen will necessarily have to be developed as

data are accrued. However, patients experiencing DLT or unacceptable toxicity will have their treatment interrupted until the toxicity returns to  $\leq$  Grade 1 or pre-treatment baseline, whichever is more severe. BVD-523 treatment may then be re-initiated at the next lower dose level which has been safely tested or at a 20–30% dose decrease, aligning with capsule dose availability. Such dose adjustments will be done in consultation with the Investigators and Medical Monitor of the study.

Each cohort can only begin when the previous cohort has completed treatment to at least the end of Week 3 without fulfilling a criterion that would prevent dose escalation.

Although dose escalation decisions may be taken upon review of the data from Cycle 1, safety data will be collected from all patients continuing treatment and 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.

In addition, once the RP2D is defined, intra-patient dose escalation to the RP2D will be allowed after a patient has completed at least one cycle at their assigned dose and only if the patient has experienced no toxicity above Grade 1, upon request by the PI and discussion with the Medical Monitor and the Sponsor.

### 8.1.3 Dosing Instructions for the Study Participants

Patients will be instructed to take their study medication twice daily at  $12 \pm 2$ -hour intervals. The study medication should be taken with 8 ounces of water at the same time each day on an empty stomach (30-60 minutes before food or 2 hours after food). All capsules, if more than one is taken at each dosing time, should be taken within 10 minutes.

#### Drug Storage

Information will be provided in the Study Manual.

#### Drug Accountability

The investigator or trial 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:

- Date received
- Lot number
- Bottle number
- Date dispensed
- Patient number
- Identification of the person dispensing the drug, with date

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

Any drug remaining in opened dispensing containers will be destroyed after the site monitor has verified drug accountability at the site, unless Institutional SOPs prohibit storage of unused or waste drug. Unused and unopened study medication will be returned by the site monitor to the Sponsor.

## **8.2 RESCUE MEDICATIONS AND CONCOMITANT TREATMENTS**

All medications administered from 28 days prior to the commencement of study treatment (Day 1) through the end of treatment 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 the 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 nonleading 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 1 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 current FDA “Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies”.

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.

### **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 provide an assessment as to whether or not the AE was related to study drug, as outlined below.

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.

## **9.7 POSTSTUDY 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., 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.

The investigator should notify Clinipace Worldwide, Inc. (CPWW) 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. 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 that the Sponsor believes have at least a reasonable possibility to be related to study drug 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. 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
- 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 serious, unexpected and to have at least a reasonable possibility of having been caused by the drug, to FDA according to 21 CFR 312.32 and current guidance. 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.

### 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 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.

## **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 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. Groups of 1–6 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 40 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).

The purpose of Part 2 of this first in human research is to document that there is some evidence of a response. Upon completion of Part 1 of this study, up to approximately 105 evaluable patients with certain cancer types and/or characterized genetic alterations and/or MAPK pathway activation will be treated with the RP2D (which may be the same or lower than the MTD). 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.

Enrollment of up to 15 evaluable patients in all cohorts provides an 80% probability of seeing at least one positive response if the true response rate is at least 10%. Allowing for a low response rate in these patient cohorts is appropriate based on unmet medical need.

Up to 15 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 will consist of all patients of the mITT population who completed the 1<sup>st</sup> protocol-specified tumor measurement evaluation (except for study drug-related AE) without major protocol violations.

### 10.2.4 Definition of Study Days

In each treatment cycle, a total of 5 visits are planned for Part 1 of this clinical study. Patients in Part 2 of the study will receive a total of up to 5 visits per treatment Cycle. The study visits are defined in Table 10.1 and summarized in Table 6.1.

**Table 10.1. Per Cycle Study Visit Definitions**

Visit Description	Study Day
Visit 1: Screening*	Day -14 to -1
Visit 2: Baseline / Randomization / 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

\*Note: informed consent may be obtained up to -28 days to allow flexibility in scheduling of the screening procedures.

## 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
- Tumor type
- Tumor mutation status

### 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 Endpoint

MTD

Please see Section 3.1.4.1 for the determination of MTD.

RP2D

Please see Section 3.1.4.3 for the determination of RP2D.

### 10.3.6 Secondary Endpoints

#### Anti-tumor Activity as Evaluated Using RECIST Criteria

Disease response will be summarized in tabular format showing the number and percent of patients in each dose level.

No formal efficacy analysis will be conducted.

### 10.3.7 Pharmacokinetic Data

#### Blood and Urine BVD-523 and Selected Metabolite Concentration Levels

Systemic BVD-523 exposure as measured in blood and urine 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/IEC 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/IEC 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/IEC 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/IEC.

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/IEC/REB 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**

<b>INHIBITORS</b>	<b>INHIBITORS</b>	<b>INHIBITORS</b>
<b>3A</b>	<b>2D6</b>	<b>1A2</b>
indinavir	bupropion	fluvoxamine
nelfinavir	fluoxetine	ciprofloxacin
ritonavir	paroxetine	enoxacin
mibedfradil <sup>1</sup>	quinidine	
clarithromycin		
itraconazole		
ketoconazole		
voriconazole		
nefazodone		
saquinavir		
telithromycin		
boceprevir		
conivaptan		
posaconazole		
telaprevir		
lopinavir/ritonavir		
Grapefruit juice <sup>2</sup>		
<b>INDUCERS</b>		
<b>3A</b>		
carbamazepine		
phenytoin		
rifampin		
Avasimibe <sup>3</sup>		
St. John's Wort <sup>4</sup>		

1. Withdrawn from the United States market because of safety reasons
2. The effect of grapefruit juices varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
3. Not a marketed drug
4. The effect of St John's wort varies widely and is preparation-dependent.

Strong Inhibitors:  $\geq 5$ -fold increase in AUC or  $> 80\%$  decrease in CL

Strong Inducers:  $\geq 80\%$  decrease in AUC

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit> Accessed 4-5-16 Table dated 10-27-14