A PHASE 1 STUDY TO INVESTIGATE THE ABSORPTION, METABOLISM, AND EXCRETION OF [^{14}C]-BVD-523 FOLLOWING SINGLE ORAL DOSE ADMINISTRATION IN HEALTHY MALE SUBJECTS

Protocol 523HV001

Covance Study 8353316

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for

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ABBREVIATIONS

% AUC_{extrap}	percentage extrapolation
% F_{ef}	percent of dose excreted in feces over sampling interval
% F_{eu}	percent of dose excreted in urine over sampling interval
A_{eu}	amount excreted in urine over sampling interval
A_{ef}	amount excreted in feces over sampling interval
AE	adverse event
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
AUC_{0-12}	area under the concentration-time curve from Hour 0 to Hour 12
AUC_{0-24}	area under the concentration-time curve from Hour 0 to Hour 24
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
BID	twice daily
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CL/F	apparent oral clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
C_t	last measurable concentration
CRU	Clinical Research Unit
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
HCl	hydrochloride
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
IRB	Institutional Review Board
λ_Z	apparent terminal elimination rate constant
MAPK	mitogen-activated protein kinase

MDS	myelodysplastic syndromes
MTD	maximum tolerated dose
PE	physical examination
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
UA	urinalysis
US	United States
V_z/F	apparent volume of distribution

1 SYNOPSIS

Title of Study:	A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-BVD-523 Following Single Oral Dose Administration in Healthy Male Subjects
Objectives:	The primary objective of this study is to characterize the metabolic disposition, pharmacokinetics (PK), and routes of elimination of [^{14}C] labeled BVD-523 after administration of a single, oral dose to healthy male subjects. The secondary objective of this study is to evaluate the safety and tolerability of a single oral dose of [^{14}C] labeled BVD-523 in healthy male subjects.
Methodology/Study Design:	This is an open-label, absorption, metabolism, and excretion study. Blood/plasma, urine, and fecal samples for bioanalytical, radioanalytical, and metabolism analysis, as applicable, will be obtained through 168 hours postdose. If Discharge occurs after Day 8, additional samples (blood/plasma, urine, and fecal) for radioanalysis will be collected every 24 hours until Discharge.
Number of Subjects:	Six healthy male subjects will be enrolled and dosed on Day 1 to complete at least 4 subjects.
Diagnosis and Main Criteria for Inclusion:	Healthy male subjects between 18 and 65 years of age, inclusive, with a body mass index of 18.5 to 32.0 kg/m^2, inclusive.
Test Product(s), Dose, and Mode of Administration:	Subjects will receive a single oral 600-mg (4 ×150-mg capsules) dose of BVD-523 containing approximately 200 μCi of [^{14}C] labeled BVD-523 following a 2-hour fast that follows breakfast.
Duration of Treatment:	Planned Enrollment/Screening Duration: up to 27 days (Days -28 to -2) Length of Confinement: up to 16 days (Day -1 to Day 15) Planned Study Conduct Duration (Screening to Discharge): up to 43 days
Criteria for Evaluation: Safety	Safety endpoints for this study include: incidence, nature, and severity of adverse events (AEs), clinically significant changes in results of clinical laboratory evaluations, vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examination (PE) findings.
Criteria for Evaluation: Pharmacokinetics	The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of BVD-523, metabolites, and total radioactivity in whole blood and plasma: maximum observed concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC from Hour 0 to Hour 12 (AUC_{0-12}), AUC from Hour 0 to Hour 24 (AUC_{0-24}), AUC extrapolated to infinity ($AUC_{0-\infty}$), percentage extrapolation (% AUC_{extrap}), apparent terminal elimination rate constant (λ_Z), terminal phase half-life ($t_{1/2}$), apparent oral clearance (CL/F; for BVD-523 only), apparent volume of distribution (V_z/F; for BVD-523 only), the ratio of AUC_{0-12} of nonradiolabeled BVD-523 in plasma to AUC_{0-12} of total radioactivity in plasma (AUC_{0-12} plasma BVD-523/Total Radioactivity Ratio), the ratio of AUC_{0-24} of nonradiolabeled BVD-523 in plasma to AUC_{0-24} of total radioactivity in plasma (AUC_{0-24} plasma BVD-523/Total Radioactivity Ratio), the ratio of $AUC_{0-\infty}$ of nonradiolabeled BVD-523 in plasma to $AUC_{0-\infty}$ of total radioactivity in plasma ($AUC_{0-\infty}$ plasma BVD-523/Total Radioactivity Ratio), the ratio of AUC_{0-12} of nonradiolabeled metabolites in plasma/AUC_{0-12} of total radioactivity in plasma (AUC_{0-12} Plasma Metabolites/Total Radioactivity Ratio), the ratio of AUC_{0-24} of nonradiolabeled metabolites in plasma/AUC_{0-24} of total radioactivity in plasma (AUC_{0-24} Plasma Metabolites/Total Radioactivity Ratio), the ratio of $AUC_{0-\infty}$ of nonradiolabeled metabolites in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma ($AUC_{0-\infty}$ Plasma Metabolites/Total Radioactivity Ratio), the ratio of $AUC_{0-\infty}$ of total radioactivity in whole blood to $AUC_{0-\infty}$ of total radioactivity in plasma ($AUC_{0-\infty}$ Blood/Plasma Ratio), the ratio of AUC_{0-12} of total

	radioactivity in whole blood to AUC_{0-12} of total radioactivity in plasma (AUC_{0-12} Blood/Plasma Ratio), and the ratio of AUC_{0-24} of total radioactivity in whole blood to AUC_{0-24} of total radioactivity in plasma (AUC_{0-24} Blood/Plasma Ratio). The following PK parameters will be calculated, whenever possible, based on the urine concentrations of BVD-523 and total radioactivity: amount excreted in urine over sampling interval (A_{eu}), cumulative A_{eu}, renal clearance (CL_R; for BVD-523 only), percent of dose excreted in urine over sampling interval (% F_{eu}), and cumulative % F_{eu}. The following PK parameters will be calculated, whenever possible, based on the fecal concentrations of total radioactivity: amount excreted in feces over sampling interval (A_{ef}), cumulative A_{ef}, percent of dose excreted in feces over sampling interval (% F_{ef}), and cumulative % F_{ef}. Metabolites of [^{14}C]-BVD-523 will be identified and characterized in plasma, urine, and feces. Pharmacokinetic parameters for the metabolites of [^{14}C]-BVD-523 will be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.
Statistical Methods:	Descriptive statistics (arithmetic mean, standard deviation, geometric mean, geometric coefficient of variation, median, minimum, maximum, and number of observations) will be calculated for the PK parameters. No formal statistical analyses are planned. Safety data (AEs, clinical laboratory data, vital signs measurements, ECG data, and PE findings) will be listed and summarized by parameters and timepoints, as appropriate.

2 INTRODUCTION

2.1 Background

BVD-523 is a small molecule inhibitor of extracellular signal-regulated kinase (ERK) family kinases (ERK1 and ERK2) that is being developed as a novel anti-cancer drug. Extracellular signal-regulated kinase family kinases are downstream components of the mitogen-activated protein kinase (MAPK) signaling cascade (RAS-RAF-MEK-ERK). Drugs that inhibit MAPK pathway components, BRAF or MEK kinases, are effective cancer therapies, but tumors often display primary and acquired resistance to these agents. The ERK kinase inhibitor BVD-523 may effectively treat both naïve and drug-resistant cancers.

BVD-523 is a potent (K_i approximately 0.04 nM for ERK2, < 0.3 nM for ERK1), selective, ATP competitive, reversible kinase inhibitor. BVD-523 demonstrates potent anti-cancer activity in in vitro cell studies, especially in cells with activating mutations in the MAPK pathway. Consistent with its mechanism, BVD-523 inhibits phosphorylation of ERK substrates and inhibited cell proliferation and survival. Importantly, BVD-523 is effective in cells that show acquired resistance to MEK kinase inhibitors; BVD-523 alone and in combination may effectively treat non-overlapping tumor drug resistance.

2.1.1 Nonclinical Data

BVD-523 shows in vivo anti-cancer activity when dosed orally in mouse xenografts dependent on ERK signaling, including models of melanoma, colon, and pancreatic cancers. Tumor biomarker effects, including protein phosphorylation and gene expression changes, occur in an exposure-dependent fashion following BVD-523 administration; biochemical and anti-tumor effects are typically observed when BVD-523 tissue concentrations exceed low micromolar concentrations, consistent with in vitro observations. These data demonstrate that BVD-523 as a single agent has anti-tumor activity in multiple cancer cell lines; doses required for efficacy are consistent with exposures required for BVD-523 to inhibit its molecular target in cell assays.

BVD-523 is highly cell permeable, a putative P-glycoprotein transporter substrate, and is highly protein bound in multiple species (96% to 100%). In vivo, the compound exhibits oral bioavailability ranging from 23% in dogs to approximately 100% in monkeys and exhibits predominantly linear dose-exposure characteristics at pharmacologically active doses. In vivo, the compound effectively distributes to multiple tissues, with initial peak concentrations highest in liver, kidney, and lung; BVD-523 was poorly distributed into

brain tissue. Radiolabeled studies in the dog with [^{14}C]-BVD-523 demonstrated metabolism in the gastrointestinal tract and/or by first-pass metabolism after absorption was the primary mechanism of clearance after an oral dose. [^{14}C]-BVD-523 underwent substantive metabolism in dogs after a single oral dose of [^{14}C]-BVD-523 to produce 5 identified/characterized radiolabeled metabolites.

BVD-523 exhibits suitable safety properties in vitro and in vivo. BVD-523 shows no significant interaction in in vitro screens against 65 receptors, transporters, and ion channels. In functional tissue assays of adenosine A1 receptor activity at concentrations up to 30 μM BVD-523 no significant response was observed, despite affinity for the human adenosine A1 receptor half maximal inhibitory concentration (IC_{50}; IC_{50} = 77 nM) in a screening assay. BVD-523 exhibits no significant genetic toxicology risks in reverse mutation and micronucleus assays. BVD-523 absorbs ultraviolet light at 320 nM; patients are being advised to limit skin exposure to light.

While BVD-523 inhibits the human ether-a-go-go related gene current (IC_{50} = 3.4 μM), dog Purkinje fiber assays revealed no significant effects up to 10 μg/mL. Additionally, no cardiovascular findings were observed in telemetered dogs receiving a single dose of BVD-523 maximum observed concentration (C_{max}; C_{max} = 17.3 μM) or in dogs after 28 days of dosing at a dose level above its 28-day maximum tolerated dose (MTD). Patients dosed with BVD-523 are being monitored for potential corrected QT interval prolongation and related cardiotoxicities.

BVD-523 does not significantly inhibit cytochrome P450 (CYP) enzymes in vitro, nor does it significantly induce CYP enzymes, either in vitro or ex vivo. The compound is metabolized via oxidation and de-alkylation, predominantly by CYP3A4, and to a lesser extent by CYP2D6 and CYP1A2. The metabolite profile of BVD-523 is very similar in mouse, rat, dog, and human assays; a disproportionate amount of a +30 amu metabolite is produced in the monkey. In preclinical studies, the disposition of BVD-523 administered orally in vivo is not significantly affected by food or gender differences. BVD-523 exhibits rapid absorption and is eliminated predominantly through hepatic mechanisms. The compound is cleared completely following dose discontinuation, and exhibits modest accumulation after repeated dosing. The compound half-life ranges from 1.1 hours in mice to 3.2 hours in dogs.

A variety of BVD-523-related toxicologic findings occurred following 28 days of dosing in Good Laboratory Practice studies conducted in rats and dogs.

In rats, BVD-523-related tissue mineralization occurs in multiple tissues in a dose-dependent fashion. Animals demonstrating mineralization following treatment with

BVD-523 exhibit significantly increased serum phosphorus and modestly decreased serum calcium. Calcium and phosphorus are being monitored during the clinical studies.

Skin lesions characterized by inflammation, dermatitis, ulceration, and acanthosis occur in rats chronically dosed with BVD-523. The incidence and severity of skin lesions are dose- and exposure-dependent, and skin toxicities are partially reversible following dose discontinuation. Additional BVD-523-related adverse findings that are partially reversible in rats include swelling in the neck; decreased forelimb strength; enlarged lymph node, spleen, and mammary gland tissues. Microscopic findings were also observed in various tissues. The tolerated dose in rats was 12.5 mg/kg twice daily (BID), with a C_{max} of 25 and 32 μg/mL, and an area under the concentration-time curve (AUC) from Hour 0 to Hour 12 (AUC_{0-12}) of 156 and 227 μg*h/mL at steady state in males and females, respectively.

BVD-523 can be dosed in dogs without severe toxicity for 28 days at 5 mg/kg BID, while doses starting at 15 mg/kg BID are toxic. Toxicity in dogs treated at 5 mg/kg BID and lower is mainly limited to the digestive tract, although additional clinical pathology (increased fibrinogen and decreased albumin) and microscopic findings (inflammation in ileum and cecum and lymphoid depletion in gut-associated lymphoid tissue) are also observed. Signs of poor health resolve following dose cessation, and additional findings are fully reversible 1 month after dose discontinuation. The tolerated dose in dogs was 5 mg/kg BID, with a C_{max} of 0.54 and 0.55 μg/mL, and an AUC_{0-12} of 3.1 and 2.9 μg*h/mL at steady state in males and females, respectively. Importantly, biomarker studies suggest significant ERK kinase inhibition occurs in peripheral blood cells of dogs treated with doses of BVD-523 that are tolerated.

2.1.2 Clinical Data

BVD-523 has been administered to 128 patients with a wide variety of solid tumors (104 patients) and myelodysplastic syndromes (MDS)/acute myelogenous leukemia (AML) (24 patients). BVD-523 is administered orally, on an empty stomach, and on a chronic basis with dosing interruptions only when necessary to manage adverse events (AEs) or to manage events related to underlying malignancy. In some, but not all instances, reinitiation of study drug after a dosing interruption for AE management has been at a reduced dose; the need for dose reduction has been at the discretion of the treating physician in consultation with the Medical Monitor. Patients were allowed to remain on study until unacceptable toxicity or until disease progression, with the majority of discontinuations thus far related to progression of the underlying malignancy.

The emerging safety profile has been largely anticipated based on the preclinical, Investigational New Drug-enabling, animal studies and on the clinical experience of other anti-cancer agents targeting components of the MAPK pathway. An MTD of 600 mg (4 x 150-mg capsules) BID was determined in patients with solid tumors and also in patients with MDS/AML, and this dose subsequently became the starting dose for all patients initiating therapy with BVD-523. Dose limiting toxicities at doses higher than the MTD included rash, vomiting, diarrhea, elevated alanine aminotransferase (ALT), elevated creatinine, hypotension, and anemia in the solid tumor study, and rash and elevated liver function tests in the MDS/AML study.

The emerging AE profile is revealing that events related to the skin and gastrointestinal tract are particularly common, as are the general disorders of fatigue, edema, and fever. Adverse events related to skin, pruritus and rash, have been common, although other less common but significant skin events have also been reported, including erythema multiforme, light sensitivity, and keratoacanthoma. Rash has been managed with topical and/or oral concomitant medications and dose interruptions and/or reductions as necessary. The gastrointestinal events of nausea, vomiting, and diarrhea have been observed commonly, in some cases occurring in association with dehydration and elevated creatinine and renal insufficiency. Nausea, vomiting, and diarrhea have been managed with study drug dosing interruptions (and/or dose reductions) and supportive medications as needed. The general events of fatigue, edema, and fever have also been managed variably with supportive medications and/or interruption of study drug administration until improvement or resolution.

Study drug-related events of elevated aspartate aminotransferase and/or ALT and elevated creatinine, while not common, have been reported and have been managed with study drug interruption and, in some instances, dose reduction or discontinuation. Other possibly related or related AEs of particular interest include ocular effects, cardiac failure, thrombotic thrombocytopenia purpura, effects on peripheral blood counts, and photosensitivity.

BVD-523 has, to date, been administered to adult patients and has not been administered in conjunction with other anti-neoplastic agents with the exception of hydroxyurea (allowed short-term in the MDS/AML study) and hormonal therapy.

Orally administered BVD-523 at doses ranging from 10 to 900 mg BID was generally slowly absorbed in patients with advanced malignancies, with individual time to maximum concentration (T_{max}) values of 2 to 8 hours at dose levels of 10 to 150 mg BID, and median T_{max} values of 3 to 4 hours at dose levels of 300 to 900 mg BID. After reaching C_{max}, plasma BVD-523 concentrations remained somewhat sustained for

approximately 2 to 4 hours. The compound half-life ranges from 9 to 11 hours. Exposure (C_{max} and AUC_{0-12}) to BVD-523, as well as selected metabolites, generally increased in a dose-related fashion from dose levels of 10 to 600 mg BVD-523 BID. At Day 1, a further increase in exposure was seen at 750 mg BVD-523 BID, but exposure was similar between 750 and 900 mg BID. At Day 15, no further increase in exposure was observed as the dose increased from 600 to 900 mg BVD-523 BID.

A single-dose, 2-way crossover study to evaluate the effects of food on the pharmacokinetics (PK), safety, and tolerability of an orally administered 600-mg dose of BVD-523 has been completed in healthy volunteers. Fourteen healthy volunteers were dosed in this study. Following single-dose oral administration of 600 mg BVD-523, the median T_{max} occurred at 3.1 hours in fasted subjects and at 6.1 hours in fed subjects (high-fat breakfast). Overall, a total of 6 treatment-emergent AEs (TEAEs) were reported in 5 subjects (35.7%). There were no deaths or serious AEs (SAEs) reported during the study and no TEAEs that led to discontinuation of subjects. All TEAEs were transient and had resolved by the end of the study.

2.2 Study Rationale

The purpose of this study is to evaluate the absorption and excretion characteristics as well as relevant PK properties of BVD-523; and to characterize and, where possible, identify the metabolites present in plasma, urine, and feces in healthy male subjects following a single dose of 600 mg (approximately 200 μCi) of [^{14}C]-BVD-523 administered as an oral dose of 4 × 150-mg capsules.

Female subjects will be excluded to align with regulatory guidance. The “as low as (is) reasonably achievable” principle prescribed by both the Food and Drug Administration (FDA) and Nuclear Regulatory Commission (2007) recommends that radiation exposure to subjects should be kept as low as is reasonably achievable; therefore, if no specific reason exists to include females (ie, no available data suggest metabolism of the study drug is different in females versus males), then the radiation exposure to female subjects should be kept at zero potential by not including females in radioactivity studies and only enrolling and dosing male subjects.

2.3 Dose Rationale

The total administered dose will be 600 mg (4 × 150-mg capsules) to ensure sufficient quantifiable concentrations of BVD-523 for determination of systemic PK. As of 16 January 2016, 27 patients have been administered BVD-523, dosed between 10 mg BID to 900 mg BID; 18 out of 27 patients received at least 600 mg BID. From this, the

MTD and recommended Phase 2 dose were determined to be 600 mg BID, which is the starting dose for all patients initiating therapy with BVD-523.

The radioactive dose will be approximately 200 μCi. This is an acceptable dose for [^{14}C]-labeled human drug metabolism studies of this type. Based on data in male Long-Evans (pigmented) rats, the overall whole-body radiation dose in a human male subject following administration of the equivalent of a single 200-μCi (7.4 MBq) dose of [^{14}C]-BVD-523 was mathematically derived from the 100-μCi dose used in the dosimetry report to be 17.1 mrem (0.1708 mSv).[1] This value is well below the FDA exposure limit of 3000 mrem after a single dose for human isotope studies. The highest calculated radiation absorbed doses following oral administration of [^{14}C]-BVD-523 were in uveal tract, epididymis, eyes, skin (pigmented), and liver in males, with values of 140.8, 29.2, 27.6, 19.0, and 14.6 mRad, respectively (1.408, 0.292, 0.276, 0.190, and 0.146 mGy, respectively). It is expected that this dose will provide a sufficient radioactive signal for total radioactivity counting and quantitative radioprofiling of [^{14}C]-BVD-523 in blood, plasma, and/or excreta with minimal radiation risk to subjects.

Please refer to the Investigator's Brochure[2] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the investigational product.

3 STUDY OBJECTIVE AND ENDPOINTS

3.1 Objectives

- The primary objective of this study is to characterize the metabolic disposition, PK, and routes of elimination of [^{14}C] labeled BVD-523 after administration of a single, oral dose to healthy male subjects.
- The secondary objective of this study is to evaluate the safety and tolerability of a single oral dose of [^{14}C] labeled BVD-523 in healthy male subjects.

3.2 Endpoints

3.2.1 Pharmacokinetic Endpoints

The PK endpoints are derived from the following biological samples and analytes:

- Plasma and urine concentrations of BVD-523;
- Plasma and whole blood concentrations of total radioactivity;
- Pharmacokinetic parameters of BVD-523 and its metabolites;

- Total radioactivity recovery in excreta (feces + urine);
- Identification and characterization of [^{14}C] labeled BVD-523 metabolites in plasma, urine, and feces.

3.2.2 Safety Endpoints

The safety endpoints for this study are:

- Incidence, nature, and severity of AEs;
- Clinically significant changes in results of clinical laboratory evaluations, vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examination (PE) findings.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This study will be an open-label, absorption, metabolism, and excretion study of [^{14}C]-BVD-523 administered as a 600-mg (approximately 200 µCi) oral dose to 6 healthy male subjects following a 2-hour fast from food (not including water) that follows breakfast.

A schematic of the study design is presented in Figure 4-1. The start of the study is defined as the date the first subject signs an Informed Consent Form (ICF). This is specifically for a subject enrolled (assigned a dose) in the study and does not include screen failure subjects for clinical pharmacology studies. A subject who completes all PK, radioactivity, and metabolism sampling prior to Discharge is considered to have completed the study. This is the last planned contact with the subject, and does not include any unplanned follow-up (eg, return to the clinic for repeat clinical laboratory). The end of the study is defined as the date the last subject completes the study. The planned duration of study conduct is up to 43 days (Screening through Discharge).

Figure 4-1 Study Design Schematic

Screening	Check-in	Dosing	PK/Radioactivity Sampling	Study Completion[a]
Days -28 to -2	Day -1	Day 1	Day 1 to Study Completion	Day 8 to Day 15
	← Confined to CRU →			

CRU = Clinical Research Unit; PK = pharmacokinetic.

[a] Subjects will be discharged from the CRU starting on Day 8 if plasma radioactivity levels are below the limit of quantitation, ≥90% of the radioactive dose is recovered, and if ≤1% of the radioactive dose is recovered in urine and feces for 2 consecutive 24-hour collection intervals. If these criteria are not satisfied

by the morning of Day 8, subjects will continue to be confined in the CRU until these criteria are met, up to a maximum of Day 15.

Subjects will be confined at the clinical site from the time of Check-in until Discharge (between Days 8 and 15). After completing discharge procedures, subjects will be discharged from the clinical site on Day 15 or as early as Day 8, provided radioactivity has reached the following threshold values:

- Plasma radioactivity levels below the limit of quantitation; and
- ≥90% of the dose is recovered; and
- Urine and fecal total radioactivity combined ≤1% of the administered dose for 2 consecutive 24-hour intervals.

Sample collection and confinement will continue until discharge criteria are met or the maximum stay is reached. Subjects experiencing emesis during the first 4 hours postdose may be discharged on the same day from the clinical site, provided there are no safety concerns, and after follow-up study procedures are performed.

In this study design, safety will be monitored with AE inquiries, clinical laboratory evaluations (Appendix A), vital signs measurements, 12-lead ECGs, and PE findings during the study.

Blood/plasma, urine, and fecal samples will be collected for bioanalytical, radioanalytical, and metabolism analysis through 168 hours postdose. If Discharge occurs after Day 8, additional samples (blood/plasma, urine, and fecal) for radioanalysis will be collected every 24 hours until Discharge. A study flow chart is presented in Table 6-1.

4.2 Discussion of Study Design

This study is designed to characterize the absorption, metabolism, and excretion of BVD-523 using radiolabeled drug in healthy adult male subjects to support its further development and registration.

The study will be conducted as an open-label trial as the study measures are objective outcomes (eg, total radioactivity in select biological matrices, metabolite profiling/characterization). Conducting the study in healthy subjects will allow the evaluation of BVD-523 metabolism in the absence of concomitant medications. The dose, subject population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

5 SUBJECT SELECTION

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

Six subjects will be enrolled to have at least 4 subjects complete the study.

5.1 Inclusion Criteria

Subjects who meet the following criteria may be included in the study:

1. Males, between 18 and 65 years of age, inclusive, at Screening;
2. Have a body mass index range of 18.5 to 32.0 kg/m^2, inclusive, at Screening;
3. In good health, determined by no clinically significant findings from medical history, 12-lead ECG, and vital signs measurements at Screening or Check-in and PE findings at Check-in as determined by the Investigator (or designee);
4. Clinical laboratory evaluations (including clinical chemistry panel [fasted at least 8 hours], hematology/complete blood count [CBC], and urinalysis [UA]; Appendix A) within the reference range for the test laboratory at Screening and Check-in, unless deemed not clinically significant by the Investigator (or designee);
5. Negative test for selected drugs of abuse and cotinine at Screening (does not include alcohol) and at Check-in (does include alcohol; Appendix A);
6. Negative hepatitis panel (including hepatitis B surface antigen and hepatitis C virus antibody) and negative human immunodeficiency virus (HIV) antibody screens (Appendix A) at Screening;
7. Males will be surgically sterile for at least 90 days (confirmed by documented azoospermia) or, when sexually active with female partners of childbearing potential, will agree to use contraception as detailed in Section 6.3.3 from Check-in until 90 days following dosing;
8. Males must be willing to refrain from sperm donation from Check-in to 90 days from the day of dosing;
9. Able to comprehend and willing to sign an ICF;
10. A minimum of 1 bowel movement per day.

5.2 Exclusion Criteria

The following will exclude potential subjects from the study:

1. Significant history or clinical manifestation of any metabolic, allergic, infectious, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator [or designee]) prior to Check-in;
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) prior to Check-in;
3. History of stomach or intestinal surgery or resection that could alter absorption or excretion of orally administered drugs prior to Check-in, except appendectomy and hernia repair will be allowed if it was not associated with complications;
4. History of Gilbert's Syndrome;
5. History or presence of an abnormal ECG that, in the Investigator's (or designee's) opinion, is clinically significant;
6. History of alcoholism or drug addiction within 1 year prior to Check-in;
7. History of nicotine use within 6 months prior to Check-in or positive cotinine at Screening or Check-in;
8. Participation in more than 1 other radiolabeled investigational study drug trial within 12 months prior to Check-in. The previous radiolabeled study drug must have been received more than 6 months prior to Check-in for this study and the total exposure from this study and the previous study will be within the recommended levels considered safe, per United States (US) Title 21 Code of Federal Regulations (CFR) 361.1 (eg, less than 3,000 mrem whole body annual exposure);
9. Exposure to significant radiation (eg, serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring) within 12 months prior to Check-in;
10. Use of any drugs or substances known to be strong inhibitors or strong inducers of CYP3A enzyme within 30 days prior to study drug administration, unless otherwise stated, and throughout the study;

11. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives (if known) or 30 days prior to Check-in, whichever is longer;
12. Use of any prescription medications/products within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee);
13. Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee);
14. Poor peripheral venous access prior to Check-in;
15. Donation of whole blood from 56 days prior to Screening through Discharge, inclusive, or of plasma from 30 days prior to Screening through Discharge, inclusive;
16. Receipt of blood products within 2 months prior to Check-in;
17. Any acute or chronic condition that, in the opinion of the Investigator (or designee), would limit the subject's ability to complete or participate in this clinical study;
18. Any other unspecified reason that, in the opinion of the Investigator (or designee) or Sponsor, makes the subject unsuitable for enrollment.

5.3 Removal of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Sponsor's Study Monitor. In case of withdrawal of study participation, efforts will be made to perform all final study day assessments (Table 6-1). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's electronic Case Report Form (eCRF). All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

The entire study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor based on the occurrence of the following:

- AEs unknown to date with respect to their nature, severity, and/or duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

A study flow chart is presented in Table 6-1. The total blood volume that will be taken during the study is outlined in Appendix B.

Table 6-1 Study Flow Chart

Study Procedures	Screening (-28 to –2)	Check-in (Day –1)	Day 1	Day 2	Day 3	Day 4	Days 5 to 7	Discharge/Early Termination (Days 8 to 15)[a]
Informed Consent	X							
Confined to the CRU		X	X	X	X	X	X	X
Demographics	X							
Medical History	X	X[b]						
Hepatitis and HIV Screen	X							
Drug Screen[c]	X	X						
Height, Weight, and BMI	X	X[d]						
12-lead ECG[e]	X	X						X
Vital Signs[f]	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluations[g]	X	X						X
Physical Examination		X						X
Dose[h]			X					
Blood Samples for PK/Radioactivity Analysis[i]			X	X	X	X	X	X
Blood Samples for Metabolism Analysis[j]			X	X	X	X	X	X
Urine Samples for PK, Radioactivity, and Metabolism Analysis[k]		X	X	X	X	X	X	X
Fecal Samples for Total Radioactivity and Metabolism Analysis[l]		X	X	X	X	X	X	X
SAE Monitoring[m]	X	X	X	X	X	X	X	X
AE Inquiry[n]		X	X	X	X	X	X	X
Previous Medication	X	X						
Concomitant Medication Monitoring		X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; CRU = Clinical Research Unit; ECG = electrocardiogram; HIV = human immunodeficiency virus; PK = pharmacokinetic; SAE = serious adverse event.

[a] Early termination procedures are to be performed in close proximity to discontinuation of subject from the study. Other procedures may be performed at Investigator (or designee) or Sponsor discretion.

[b] Interim medical history only.

[c] Drug screen does not include breath alcohol testing at Screening and does include breath alcohol testing at Check-in.

[d] Height and BMI measured at Screening only.

[e] Twelve-lead ECG will be collected after the subject has rested in the supine position for at least 5 minutes.

[f] Vital sign measurements (oral body temperature, respiratory rate, and seated blood pressure and pulse) obtained at Screening, Check-in, 0 Hour (predose); 2, 4, and 24 (Day 2) hours postdose; and daily (24-hour intervals) up to and including day of discharge. Vital signs measurements should be carried out prior to having blood drawn, except at Screening and Day -1. Vital signs will be measured after the subject has been seated for at least 5 minutes.

[g] Clinical chemistry panel (fasted at least 8 hours), complete blood count, and urinalysis.

[h] Single oral dose of [^{14}C]-BVD-523 at 600 mg (approximately 200 µCi) administered orally after a 2-hour fast that follows breakfast.

[i] Blood samples for PK and radioanalysis collected at 0 Hour (predose); 30 minutes postdose; and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose (Day 8). If subject is not discharged on Day 8, additional blood samples will be collected for radioanalysis every 24 hours until Discharge.

[j] Blood samples for metabolite profiling and identification collected at 0 Hour (predose); 30 minutes postdose; and 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose (Day 8).

[k] Urine samples collected at -12 to 0 (predose, the last void within 1 hour prior to dosing), 0 to 6, 6 to 12, and 12 to 24 hours postdose; and 24-hour intervals until Discharge.

[l] Fecal samples collected predose (within 24 hours of dosing, if possible), from 0 to 24 hours postdose, and 24-hour intervals until Discharge.

[m] Any SAEs occurring after the subject signs the Informed Consent Form will be collected.

[n] Subjects will be monitored for AEs beginning at initiation of study drug. An AE inquiry will be performed at Check-in and at each postdose vital sign measurement.

6.2 Study Treatment

6.2.1 Drug Supplies and Accountability

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drug (Table 6-2).

Table 6-2 Study Drugs

Study Drug	[^{14}C]-BVD-523
Form[a]	Blended crystalline solid
Specific Activity[b]	approximately 0.31 µCi/mg (HCl salt)
Supplier	EAG Laboratories
Manufacturer	EAG Laboratories

[a]Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug(s).

[b]Specific Activity is calculated based on the mass of the hydrochloride (HCl) salt. The oral dose of 600 mg will be based on the free base content of the drug.

The lot numbers for the study drugs will be provided to the clinical site by the supplier/manufacturer as soon as available.

Radiolabeled study drug will be stored in a freezer set to maintain a temperature of -20°C.

The Investigator (or designee) will maintain an accurate record of the receipt of the clinical trial materials as shipped by the Sponsor (or designee), including the date

received. One copy of this receipt will be returned to the Sponsor when the contents of the shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor on request.

At the completion of the study, all unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinical site, per the Sponsor's (or designee's) written instructions.

6.2.2 Subject Number and Identification

Subjects will be assigned a number by clinical site staff. Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will be enrolled only if deemed necessary by the Sponsor. Replacement subjects will be assigned a subject number by adding 100 to the number of the subject they are replacing (eg, Subject No. 105 replaces Subject No. 005).

6.2.3 Dose Preparation and Administration

Each unit dose will be prepared by qualified clinical staff. Each unit dose container will be appropriately labeled.

Appropriate unit doses, as described above, will be administered to consecutively-numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the eCRFs.

Each dose will be administered orally with approximately 240 mL room temperature water. A hand and mouth check will be performed to verify that the dose administered was swallowed. After a 2-hour fast from food (not including water) that follows a standard high-fiber breakfast, doses will be administered. After a 1-hour fast from food (not including water) that follows dosing, a snack will be served. During the study, subjects may consume water ad libitum.

Except when they are using the toilet, study subjects will be observed for approximately 4 hours postdose. Note: Amount of time corresponds to the time postdose in which subjects with emesis could be replaced and is to ensure that they are not having AEs or becoming nauseated. Subjects will not lay supine for 1 hour following dose administration, except as necessitated by the occurrence of an AE(s) and/or study procedures.

6.2.4 Blinding

This is an open-label study.

6.3 Study Restrictions

6.3.1 Diet, Fluid, and Activity Control

Subjects are required to refrain from use of tobacco- or nicotine-containing products within 6 months prior to Check-in until Discharge.

Subjects are required to abstain from consuming alcohol-, grapefruit-, or caffeine-containing foods and beverages for 48 hours prior to Check-in until Discharge, unless deemed acceptable by the Investigator (or designee).

Subjects will refrain from strenuous exercise from 72 hours prior to Check-in and during the period of confinement at the clinical site and will otherwise maintain their normal level of physical activity throughout the entire study (ie, will not begin a new exercise program or participate in any unusually strenuous physical exertion).

While confined at the clinical site, subjects will receive a standardized high-fiber diet at scheduled times that do not conflict with other study-related activities. Prune juice may be administered on an as-needed basis to aid in normal bowel function.

6.3.2 Concomitant Medications

Subjects will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurred within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in through Discharge.

Subjects will also refrain from the use of any prescription medications/products during the interval from 14 days prior to Check-in through Discharge, unless deemed acceptable by the Investigator (or designee). In addition, subjects will refrain from the use of any over-the-counter, nonprescription medications (including vitamins, minerals, and

phytotherapeutic/herbal/plant-derived preparations) from 7 days prior to Check-in through Discharge, unless deemed acceptable by the Investigator (or designee).

Subjects will not be allowed to consume any drugs or substances known to be strong inhibitors or strong inducers of CYP3A enzyme within 30 days prior to study drug administration and, unless otherwise stated, throughout the study.

A mild laxative (eg, Milk of Magnesia®, Colace®) may be used to help with bowel movements if necessary. Up to 2 grams per day of acetaminophen may be administered if approved by the Investigator (or designee). The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the study and the reason for its use will be documented in the source documents and the eCRF.

6.3.3 Contraception

Males will be surgically sterile for at least 90 days (confirmed by documented azoospermia) or, when sexually active with female partners of childbearing potential, will be required to use the following form of contraception from Check-in until 90 days following dosing: male condom with spermicide.

Males will refrain from sperm donation from Check-in until 90 days following the day of dosing.

6.4 Pharmacokinetic, [^{14}C] Radioactivity, and Metabolism Procedures

6.4.1 Blood Sample Collection for Pharmacokinetic, [^{14}C] Radioactivity, and Metabolism Analysis

Blood samples for analysis of BVD-523, total radioactivity, and metabolite profiling and identification will be collected via direct venipuncture. Blood samples will be collected at the timepoints specified in Table 6-1.

6.4.2 Urine Sample Collection for Pharmacokinetic, [^{14}C] Radioactivity, and Metabolism Analysis

Urine samples for analysis of BVD-523, total radioactivity, and metabolite profiling and identification will be collected during the time intervals specified in Table 6-1. Subjects will be encouraged to completely void urine immediately prior to the end of each respective collection interval.

6.4.3 Fecal Sample Collection for [^{14}C] Radioactivity and Metabolism Analysis

Fecal samples for total radioactivity and metabolite profiling and identification will be collected during the time intervals specified in Table 6-1.

6.4.4 Emesis Sample Collection

For subjects experiencing emesis within 4 hours following dosing, vomitus will be collected. Attempts will be made to collect vomitus from subjects experiencing emesis after 4 hours postdose. All vomitus collected will be stored for possible analysis. The time and date of collection will be recorded on the subject's source documents and eCRF. Vomitus will be analyzed as deemed appropriate.

6.4.5 Bioanalytical Methodology

BVD-523 and metabolite(s) concentrations in plasma, BVD-523 concerntrations in urine, and total radioactivity concentrations in whole blood, plasma, urine, and feces will be determined via established analytical procedures. Profiling and characterization of metabolites in plasma, urine, and feces will be conducted using standard laboratory procedures. Specifics of the analytical methods will be provided in a separate document (ie, the laboratory manual[s]).

6.5 Safety Procedures

Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Dosing
- PK blood sampling
- Start and end of urine and feces collections (for drug assay)
- Vital signs measurements
- ECGs
- Blood and urine samples for clinical laboratories
- PEs

6.5.1 Adverse Events

Adverse event definitions; assignment of severity, causality, action taken, and outcome; and procedures for reporting SAEs are detailed in Appendix C.

Subjects will be asked a nonleading question such as "Have there been any changes in your health status since Screening/since you were last asked?" at the timepoints specified in Table 6-1 to assess for the occurrence of AEs. Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study.

All nonserious AEs, whether volunteered, elicited, or noted on PE, will be recorded from initiation of study drug until study completion. Nonserious AE information observed before dosing will not be listed as an AE in the eCRF but will be listed as medical history instead, unless the AE becomes more severe postdose, in which case it will be recorded as an AE in the eCRF. Serious AEs will be recorded from the time the subject signs the ICF until study completion.

All AEs (nonserious and serious) should be followed until the event has resolved, returned to baseline, or is assessed as stable by the Investigator (or designee).

6.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including clinical chemistry panel [fasted at least 8 hours], CBC, and UA; Appendix A) will be collected at the timepoints specified in Table 6-1.

Screens for a hepatitis panel and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse (not including alcohol) will be performed at Screening and repeated (including alcohol) at Check-in.

6.5.3 Vital Signs

Vital signs measurements (including oral body temperature, respiratory rate, and seated, blood pressure and pulse) will be obtained at the timepoints specified in Table 6-1. Vital signs will be measured after the subject has been seated for at least 5 minutes.

6.5.4 Twelve-lead Electrocardiograms

A 12-lead ECG will be obtained at the timepoints specified in Table 6-1. Subjects will be supine for at least 5 minutes prior to obtaining an ECG measurement.

Electrocardiogram parameters (including heart rate; PR, QRS, and QT intervals; and QT interval corrected for heart rate using Fridericia's formula) and the Investigator's overall interpretation of the ECG will be recorded in the eCRF.

6.5.5 Physical Examinations

A routine PE will be performed at the timepoints specified in Table 6-1.

The time and date of the PE will be recorded in the eCRF and any clinically significant findings will be recorded as AEs.

7 DATA ANALYSES AND SAMPLE SIZE

7.1 Sample Size

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations. No formal statistical hypotheses are planned to be tested in this study.

7.2 Study Populations

The PK population will consist of all subjects who receive study drug and have evaluable PK data.

The safety population will consist of all subjects who receive study drug and have at least 1 postdose safety assessment.

The all subjects population will consist of all subjects who are enrolled in the study (signed the ICF) and have study assessments recorded in the eCRF. The all subjects population will be consistent with the safety population.

7.3 Pharmacokinetic Analysis

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentrations of BVD-523, metabolites, and total radioactivity in whole blood and plasma, according to the model independent approach[3]:

C_{max}	maximum observed concentration
T_{max}	time to maximum concentration
AUC_{0-t}	area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to the last measurable concentration

AUC_{0-12} area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to Hour 12

AUC_{0-24} area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to Hour 24

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, calculated using the formula:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$$

where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant

% AUC_{extrap} percentage extrapolation

λ_Z apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

$t_{1/2}$ terminal phase half-life, where $t_{1/2}$ = natural log (2)/λ_Z

CL/F apparent oral clearance (for BVD-523 only)

V_Z/F apparent volume of distribution (for BVD-523 only)

$AUC_{0-\infty}$ Blood/Plasma Ratio

$AUC_{0-\infty}$ of total radioactivity in whole blood/$AUC_{0-\infty}$ of total radioactivity in plasma

$AUC_{0-\infty}$ Plasma BVD-523/Total Radioactivity Ratio

$AUC_{0-\infty}$ of nonradiolabeled BVD-523 in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma

AUC_{0-12} Blood/Plasma Ratio

AUC_{0-12} of total radioactivity in whole blood/AUC_{0-12} of total radioactivity in plasma

AUC_{0-12} Plasma BVD-523/Total Radioactivity Ratio

AUC_{0-12} of nonradiolabeled BVD-523 in plasma/AUC_{0-12} of total radioactivity in plasma

AUC_{0-24} Blood/Plasma Ratio

AUC_{0-24} of total radioactivity in whole blood/AUC_{0-24} of total radioactivity in plasma

AUC_{0-24} Plasma BVD-523/Total Radioactivity Ratio

AUC_{0-24} of nonradiolabeled BVD-523 in plasma/AUC_{0-24} of total radioactivity in plasma

$AUC_{0-\infty}$ Plasma Metabolites/Total Radioactivity Ratio

$AUC_{0-\infty}$ of nonradiolabeled metabolites in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma

AUC_{0-12} Plasma Metabolites/Total Radioactivity Ratio

AUC_{0-12} of nonradiolabeled metabolites in plasma/AUC_{0-12} of total radioactivity in plasma

AUC_{0-24} Plasma Metabolites/Total Radioactivity Ratio

AUC_{0-24} of nonradiolabeled metabolites in plasma/AUC_{0-24} of total radioactivity in plasma

In addition, the following PK parameters will be calculated, whenever possible, for each subject based on the urine concentrations of BVD-523 and total radioactivity:

A_{eu} amount excreted in urine over sampling interval

Cumulative A_{eu} cumulative amount excreted in urine, calculated as the sum of the amount excreted in urine for each collection period

CL_R renal clearance, where $CL_R = A_e/AUC_{0-\infty}$ (for BVD-523 only)

% F_{eu} percent of dose excreted in urine over sampling interval, where % Excreted = 100 (A_{eu}/dose)

Cumulative % F_{eu} cumulative percent of dose excreted in urine, calculated as the sum of the percent of dose excreted in urine for each collection period

The following PK parameters will be calculated, whenever possible, for each subject based on the fecal concentrations of total radioactivity:

A_{ef} amount excreted in the feces over sampling interval

Cumulative A_{ef} cumulative amount excreted in feces, calculated as the sum of the amount excreted in feces for each collection period

% F_{ef} percent of dose excreted in feces over sampling interval, where % Excreted = 100 (A_{ef}/dose)

Cumulative % F_{ef}

	cumulative percent of dose excreted in feces, calculated as the sum of the percent of dose excreted in feces for each collection period

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix™ WinNonlin® (Certara USA, Inc., Version 6.4 or higher).

Pharmacokinetic parameters for the metabolites of [^{14}C]-BVD-523 may be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.

Appropriate analyte ratios will be based on relevant AUC values. Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded in the eCRF. Other data handling procedures will be detailed in the SAP.

7.4 Statistical Analysis of Pharmacokinetic Data

Descriptive statistics (arithmetic mean, standard deviation, geometric mean, geometric coefficient of variation, median, minimum, maximum, and number of observations) will be calculated for the PK parameters. No formal statistical analyses are planned.

Specification of PK parameters for analysis; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of subjects to be included in the analyses population(s), as applicable, will be presented in the Clinical Study Report and/or SAP as appropriate.

7.5 Statistical Analyses of Safety Data

Descriptive statistics will be calculated on the safety parameters. No formal statistical analyses are planned. Baseline will be defined as the last result prior to the dose of study drug, including any unscheduled predose measurements. Clinical laboratory data, vital signs, PE results, and ECG data will be listed and summarized by parameters and timepoints, as appropriate.

7.6 Data Handling and Record Keeping

Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the

reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the clinical site and verified by the Study Monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by Data Management and will be reviewed by the Covance scientific team. The eCRF and ancillary data will be converted into final SAS datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified using Web Submission Data Manager®, while the dataset content will be peer-reviewed by an independent programmer.

The tables, figures, and listings will be programmed per the final SAP. All tables, figures, and listings will be peer-reviewed by an independent programmer. In addition, draft tables, figures, and listings will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer-review will be performed by independent programmers following the quality control process and programming checklists.

7.7 Quality Control and Quality Assurance

Quality control and quality assurance will be performed according to Covance standard operating procedures or per client request and as applicable according to the contract between Covance and the Sponsor.

8 ADMINISTRATIVE ASPECTS

8.1 Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the Institutional Review Board (IRB; see Form FDA 1572).

8.2 Site Initiation Visit/Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator and appropriate clinical staff to familiarize the Investigator and clinical staff with the materials necessary for conducting the clinical study.

8.3 Disclosure

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, in part or in total (eg, articles in journals or newspapers, oral presentations, abstracts) by the Investigator or their representative(s), shall require prior notification and review, within a reasonable timeframe, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

8.4 Monitoring

The Sponsor will designate a Sponsor's Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the clinical site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

8.5 Institutional Review Board

In accordance with US Title 21 CFR 56, the protocol, advertisement, ICF, and other information provided to subjects will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator (or designee) to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the

protocol and the written ICF statement will be transmitted to the Investigator (or designee).

The IRB will be informed by the Investigator (or designee) of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator (or designee). If requested, the Investigator (or designee) will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The Investigator (or designee) will provide the IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

8.6 Informed Consent

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign 2 copies of the ICF. One copy will be given to the subject, and the other will be maintained with the subject's records.

8.7 Records

The results from data collected at Screening and during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor (or designee). Copies of each eCRF will be retained by the Investigator (or designee). All source documents, records, and reports will be retained by the clinical site in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (eg, laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the clinical site archives.

8.8 Reference to Declaration of Helsinki/Basic Principles

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), Applications for FDA Approval to Market a New Drug (21 CFR 314), and Radioactive Drugs For Certain Research Uses (21 CFR 361.1), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Conference on Harmonisation Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

8.9 Financing and Insurance

Financing and insurance will be addressed in a separate agreement.

INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

Irene Mirkin, MD
Principal Investigator
Covance Clinical Research Unit, Inc.

07 Dec 2016
Date

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to the conduct of the study as described herein:

Deborah L. Knoerzer, MS
Associate Director, Translational Sciences
BioMed Valley Discoveries Inc.

12/8/16
Date

REFERENCES

1. Fitzsimmons ME and Oswald J. Covance 8336350. *Tissue Distribution of Radioactivity After a Single Oral Dose of [^{14}C]BVD-523 to Pigmented Rats*. Covance, Inc.; Madison, Wisconsin (2016).
2. Investigator's Brochure, BVD-523. Version 3.0, 17 June 2016.
3. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd edition. New York, NY: Marcel Dekker Inc.; 1982.

APPENDIX A - CLINICAL LABORATORY EVALUATIONS

Clinical Chemistry Panel (Fasted):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Bilirubin (direct, indirect and total)
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Glucose
Iron
Phosphorus
Potassium
Sodium
Total protein
Triglycerides
Uric acid

Complete Blood Count:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (absolute):
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive)

Drug Screen:
Including but not limited to the following:
Alcohol (ethanol, via breathalyzer, at Check-in only)
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine

Other Tests:
Hepatitis B surface antigen
Hepatitis C virus antibody
HIV antibody

APPENDIX B - BLOOD SAMPLING SUMMARY

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Serology	4	1	4
Clinical Laboratory Tests	8	3	24
Sampling for Pharmacokinetic Analysis	3	17	51
Sampling for Total Radioactivity Analysis	4	24	96
Sampling for Metabolism Analysis	10	17	170
Total			**345 mL**

APPENDIX C - ADVERSE EVENTS

1 ADVERSE EVENTS

1.1 Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug-related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- Unfavorable changes in general condition;
- Subjective or objective signs/symptoms;
- Concomitant diseases or accidents;
- Clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including clinically significant laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs.

1.2 Categorization of Adverse Events

The severity of AEs will be categorized as follows:

- **MILD** = of little concern to the subject and/or of no clinical significance, is not expected to affect the subject's health or well-being;
- **MODERATE** = discomforting enough to cause interference with or change in usual activities, is likely to require medical intervention or close follow-up;
- **SEVERE** = incapacitating or causing inability to work or participate in many or all usual activities, is of concern to the subject or poses substantial risk to the subject's health or

well-being, is likely to require medical intervention or close follow-up.

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **NOT RELATED** = an AE that does not follow a reasonable temporal sequence from administration of the drug and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment;
- **UNLIKELY RELATED** = an AE that follows a reasonable temporal sequence from the administration of the drug (including after withdrawal of the drug) and cannot be excluded as being possibly caused by the drug (eg, existence of similar reports attributed to the suspected drug and/or its analogues, reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable;
- **POSSIBLY RELATED** = an AE that follows a reasonable temporal sequence from administration of the drug (including after withdrawal of the drug) and can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment;
- **RELATED** = an AE that follows a reasonable temporal sequence from administration of the drug (including after withdrawal of the drug), follows a known or hypothesized cause-effect relationship, and (if appropriate) satisfies the following:
  - Positive results obtained in drug sensitivity tests;
  - Toxic level of the drug present in blood or other body fluids.

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

The following categories will be used for the action taken with the study drug for the AE: drug withdrawn, dose not changed, drug interrupted, unknown, and not applicable.

The following categories will be used for the outcome of the AE: resolved, resolved with sequelae, ongoing, fatal, and unknown.

1.3 Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported immediately to the Investigator (or designee) and the Sponsor, including pregnancy in female partners of male subjects. Pregnancy should be reported to the Sponsor's safety representative using the Pregnancy Form provided within 24 hours of knowledge of the diagnosis.

The pregnancy may be followed to term or outcome and this outcome may be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an AE or serious AE (SAE) unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication or method.

1.4 Definition of Serious Adverse Events

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience (ie, places the subject, in the view of the Investigator [or designee], at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All SAEs must be collected that occur after the subject signs the ICF.

All SAEs must be reported to the Sponsor and the Sponsor's safety representative within 24 hours of first knowledge of the event by study personnel. Serious AEs must be

reported on the SAE Form provided by the Sponsor and submitted to the Sponsor's safety representative via email to: safety@clinipace.com

A representative from the Sponsor's safety team may contact the site for clarification of data entered onto the SAE Form, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact the Sponsor's safety representative at: safety@clinipace.com

1.5 Unexpected Adverse Drug Experience

An unexpected adverse drug experience is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure (IB) or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

1.6 Reporting

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the clinical site to the Sponsor, Medical Monitor assigned by the Sponsor, and the responsible Institutional Review Board (IRB).

The Sponsor and Sponsor's Representatives and Medical Monitor will be notified in writing within 24 hours of when an SAE that is potentially FDA-reportable is first recognized or reported using the SAE Form provided by the Sponsor.

Contact Information for Safety Reporting
Safety Associate Clinipace Worldwide, Inc. safety@clinipace.com

Subsequently, a written confirmation or summary of the SAE (using FDA Form 3500A, or equivalent) will be sent to the Sponsor within 3 working days of the original notification. (Instructions for completion of FDA Form 3500A may be obtained from the FDA website at www.fda.gov/medwatch/how.htm.)

The IRB will be notified of any FDA-reportable AE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

The Sponsor or the Sponsor's safety representative is responsible for submitting reports of AEs associated with the use of the drug that are serious, unexpected, and thought to have at least a reasonable possibility of having been caused by the drug, to the FDA according to 21 CFR 312.32 and current guidance.