BIOMED VALLEY
DISCOVERIES

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PROTOCOL NUMBER:	BVD-523-01
	PHASE 1 DOSE-ESCALATION, SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF BVD-523 IN PATIENTS WITH ADVANCED MALIGNANCIES
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CR	Complete Response
eCRF	electronic Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicities
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ITT	Intent-to-Treat
Min	Minimum
MITT	Modified Intent-to-Treat
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
PD	Progressive Disease
PE	Physical Examination
PK	Pharmacokinetics
PR	Partial Response
PP	Per-Protocol
PT	Preferred Term
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
SMC	Safety Monitoring Committee
TEAE	Treatment Emergent Adverse Event
VS	Vital Signs
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol BVD-523-01. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection.

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary Objectives

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).

A DLT is defined (per definition in protocol amendment 7)[1] as a **BVD-523 related toxicity** in the first 21 days of treatment that results in:

- ≥ Grade 4 hematologic toxicity for > 1 day;
- Grade 3 hematologic toxicity with complications e.g., thrombocytopenia with bleeding;
- ≥ Grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the adverse event (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.

[1] The original protocol, as well as amendments 1, 2, 3, and 4 defined DLTs slightly differently. In these amendments, a DLT was defined as above except for the following:

- ≥ Grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the adverse event (AE) persists despite adequate treatment)
- "A doubling of AST/ALT in patients with grade 2 ALT/AST at baseline" was introduced in Amendment 5

Treatment interruption DLTs were also defined slightly differently in different protocols:

- For the original protocol and Amendments 1 & 2: A treatment interruption exceeding 3 days in Cycle 1 due to drug-related toxicity (or inability to begin Cycle 2 for > 7 days) due to drug-related toxicity.
- For Amendment 3: A treatment interruption exceeding 5 days in Cycle 1 due to drug-related toxicity (or inability to begin Cycle 2 for > 7 days due to drug-related AE)
- For Amendment 4, 5, 6 & 7: 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.

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

2.1.2 Secondary Objectives

Secondary objectives of this study are:

- 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)

2.1.3 Exploratory Objectives

- To evaluate pharmacodynamic marker (biomarker) measures
- To investigate any preliminary clinical effects on tumor response assessed by FDG-PET radiological exam.

  According to the Note to File signed (11/02/2015), FDG-PET is no longer collected. At Amendment 7, the language was officially removed from the protocol.

2.2 TREATMENT GROUPS

Treatment groups of the study consist of various dose level cohorts (starting at 10 mg twice daily (bid) for 21 days (a "Cycle")) used in the dose-escalation phase of the study and the group number (Group 1 - Group 7 as specified in Section **Error! Reference source not found.**) used in the cohort expansion phase of the study and dosed at the RP2D.

2.3 STUDY ENDPOINTS

2.3.1 Primary Endpoints

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

2.3.2 Secondary Endpoints

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 [Response Evaluation Criteria In Solid Tumors] version 1.1)

2.3.3 Exploratory Endpoints

Pharmacodynamics: Evaluation of multiple biomarkers to characterize response to drug (pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA). Additional biomarkers may be identified during the study 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 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

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. It will be conducted at up to 15 sites. This clinical study comprises 2 parts: Part 1: Dose-escalation Phase and Part 2: Cohort Expansion Phase.

Part 1: Dose-escalation Phase, An accelerated dose escalation plan will be used to establish DLT, MTD, and the 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. Up to 40 patients will be enrolled in Part 1. 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 cohorts design, followed by a standard 3 + 3 design, informed by the accrued safety experience throughout the study (see Table 1 below). All dose-escalation decisions will be based on Cycle 1 safety data. 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. Doses will not be escalated unless the patient(s) receiving the highest current dose has been observed for at least 3 weeks. No intra-patient dose escalation was permitted under the original protocol or the first two amendments. Starting under amendment three, intra-patient dose escalations were allowed; see protocol for details.

Once the RP2D is defined, intra-patient dose escalation to the R2PD 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.

Table 1: Summary of Dose Escalation

Single Patient Cohorts	
Observed Safety Outcomes	**Action**
AEs ≤ Gr 1	• Continue testing with single patient cohorts • Escalate by 100% to next dose level
One AE ≥ Gr 2 (excluding alopecia or diarrhea)	• Expand current and subsequent cohorts to ≥ 3 patients • Escalate by ≤ 50% to next dose level
1 DLT	• Expand cohort up to 6 patients
Standard Escalation Cohorts (3–6 patients)	
Observed Safety Outcomes	**Action**
No DLTs	• Escalate by ≤ 50% to next dose level
1 DLT in 3 patients	• Expand cohort up to 6 patients
1 DLT in 6 patients	• Escalate by ≤ 50% to next dose level
> 1 DLT in ≤ 6 patients	• Stop dose escalation

When more than 1 DLT occurs in ≤ 6 patients in a dosing cohort, dose escalation will be stopped and this dose level will be identified as a non-tolerated dose. Doses between the non-tolerated dose and the preceding lower dose, where ≤ 1 DLT occurred, may be explored to define the MTD.

In Part 2 – Cohort-expansion Phase, an additional (approximately 105) patients with particular tumor types and/or cancers harboring specific genetic mutations (as specified in patient groups 1-7 below) will be recruited for treatment at the 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. Treatment cycles will occur consecutively without interruption except when necessary to manage toxicities. Intra-patient dose modifications are allowed, including dose reductions/interruptions as needed and re-escalations up to and including RP2D, at Clinical Investigator's discretion.

- 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

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 serious adverse event (SAE) occurs at any time during the study, the Safety Monitoring Committee (SMC) 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.

3.2 SCHEDULE OF STUDY ASSESSMENTS

Table 3.1. Table of Study Assessments

The schedule of study assessments and procedures for patients in both Part I and Part II of the study is shown below:

		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21 day cycles, visit on 1st day of cycle	
Visit	**1 Screening**	**2 Baseline**	**3 Tx**	**4 Tx**	**5 Tx**	**6 Tx**	**7 Tx**	**8 -X Tx**	**Final Study Visit/ Early Discontinuation**
Visit Day	-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[1]	X[9]	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[2]	X								X
Pregnancy test[3,4]	X	X[3]			X[4]			X[4]	X[4]
Study drug dispensed		X	X	X	X	X	X	X	
Study drug administration[5]		X	X	X	X	X	X	X	
Pharmacokinetic samples[6,7]		X[7]		X[6]	X[6]				
Pharmacodynamic samples[6,7,8]		X[7]		X[6]					
Tumor measurements[9]	X							X	X
Clinical lab tests[10]	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)[11]	X		X						
Holter monitoring[12]		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.

1 Full medical history at screening, review/update of history only at subsequent visits.

2 Ophthalmological examinations will be performed by an ophthalmologist at screening, at End of Treatment and if clinically indicated.

3 ONLY if the screening serum pregnancy test was performed more than 1 day previously.

4 After screening and baseline, urine pregnancy test which if positive, confirm with serum test.

5 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.

6 In Part 1PK 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 ± 5 minutes), 2 hours, 4 hours, 6 hours, 8 hours (all ± 10 minutes), and 12 hours (± 2 hours) post first dose. Blood samples for pharmacodynamic assessment will be collected pre-dose and 4 hours post–dose (±10 minutes). PK urine samples will be collected prior to first dose and for the 1–6-hour and 6–12 ± 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.

7 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 and/or after disease progression.

8 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.

9 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 1st 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.

10 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.

11 Patients with a normal ECG in Cycle 1 need not have repeat ECGs in subsequent cycles.

12 Holter monitoring for 12±2 hours during PK sampling.

4 SAMPLE SIZE CONSIDERATIONS

For this Phase 1 dose escalation study, no formal sample size calculations have been performed; the sample size reflects practical considerations.

Approximately 40 patients will be treated in Part 1 of this study (dose-escalation phase) to establish DLT, MTD, and the RP2D.

After the completion of Part 1 of this study, up to 105 additional 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) to determine if BVD-523 is effective as a single agent therapy. The purpose of the second phase of this first in human research is to merely document that there is some evidence of a response (complete response or partial response per RECIST v 1.1).

5 ANALYSIS POPULATIONS

Five analysis populations will be used to analyze the study data. Below are details of each analysis population:

5.1 SAFETY

The Safety Population consists of all patients receiving at least one dose of study medication.

This population will be used to summarize demographics and baseline characteristics, previous and concomitant medication/therapies, treatment exposure and all safety endpoints including AE, physical examination (PE), ophthalmology examination, clinical laboratory tests (chemistry, hematology, and urinalysis), serum/urine pregnancy test, ECG, Holter monitoring, and vital signs (VS).

5.2 MODIFIED INTENT-TO-TREAT

The modified Intent-To-Treat (mITT) Population is defined as all patients receiving at least one dose of study medication. Subject demographics, disposition, and analysis population summaries will be tabulated using the mITT population.

5.3 PER-PROTOCOL

The Per Protocol population consists of all patients from the modified ITT Population who have completed the first protocol-specified tumor measurement evaluation (except for study drug-related AE) without major protocol violations. All protocol deviations will be reported, but prior to generating TFLs for either Part 1 or Part 2, the list of protocol deviations will be reviewed and each classified as either major or minor. This population will be used to summarize clinical effects on tumor response using RECIST version 1.1 criteria. Analyses based on the PP population will be exploratory.

5.4 PHARMACOKINETIC

The Pharmacokinetic (PK) Population is comprised of all patients who receive at least 1 dose of study drug and have sufficient and valid PK samples to estimate PK parameters ($C_{max,}$ $t_{max,}$

$AUC_{0\text{-}12}$, $AUC_{0\text{-}last}$, λ_z, $t_{1/2}$) for Day 1 and/or Day 15. In Part 2, urine PK samples were not collected so urine PK analyses will only be presented for Part 1 subjects.

Pharmacokinetic summaries will be based on the PK population (refer to Section 11.1 of this SAP).

5.5 PHARMACODYNAMIC

The Pharmacodynamics (PD) Population is defined as patients in the Safety Population who provide at least one pharmacodynamic measurement from fluid and/or tumor samples for Day 1 or Day 15, relative to pre-treatment levels.

All pharmacodynamics data will be analyzed based on the pharmacodynamics population.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 PROGRAMMING ENVIRONMENT

All analyses will be conducted using SAS® version 9.2 or higher.

6.2 STRATA AND COVARIATES

Not applicable.

6.3 SUBGROUPS

The only planned subgroup analyses are the seven patient subgroups from Part 2 (see Section 3.1 of this SAP).

6.4 MULTIPLE COMPARISONS AND MULTIPLICITY

There are no planned adjustments for multiplicity.

6.5 SIGNIFICANCE LEVEL

Unless otherwise noted, all statistical analyses will be conducted using the significance level (α) of 0.05 and utilize two-sided testing. However, no inferential testing is prospectively planned for the current study data.

6.6 STATISTICAL NOTATION AND METHODOLOGY

Unless stated otherwise, the term "descriptive statistics" refers to the number of patients (n), mean, median, standard deviation (STD), minimum (Min), and maximum (Max) for continuous data and frequencies and percentages for categorical data. Min and Max values will be presented using the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and STDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number. For percentage values that are less than 1% but greater than 0%, they will be presented as "< 1%". Similarly, "> 99%" will be used to display percentages that are greater than 99% but less than 100%. P-values will be presented with 3 decimal places and values less than 0.001 will be presented as < 0.001.

All data collected during the study will be included in data listings and will be displayed and sorted by study part, dose level, cohort/treatment group, patient number and then by date/time (including visit, cycle, and day), if any, for each patient number, unless otherwise noted.

7 DATA HANDLING METHODS

7.1 MISSING DATA

7.1.1 Date Values

In cases of incomplete dates (e.g., pertaining to AE, concomitant medication, medical history, etc.), the missing component(s) will be assumed as the most conservative value(s) possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations (i.e., treatment-emergent status, etc.). If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

7.1.2 Non-Date Values

Every effort will be made to obtain the protocol-required data for all study assessments that are scheduled for each scheduled visit for all subjects who have been enrolled. No data imputation will be applied to missing study data except for imputing visit dates to classify AE and concomitant medication data into the study phase of "pre-treatment," "during treatment," or "post-treatment."

7.2 VISIT WINDOWS

All study data will be presented at the nominal visit obtained from the eCRFs, if available. Study day is defined as (date of visit – date of treatment initiation + 1). That is, study day 1 indicates the date of treatment initiation. In the case of early termination visit, date of the visit will be used to calculate the nominal visit for the analysis.

If there are two or more assessments within a nominal visit, then the assessment that is closest to the scheduled time point/target day will be used in the analysis. If there is more than one closest value, then the evaluation occurring after the target day and prior to the date of last dose will be used in the analysis.

All values will be included in the data listings.

7.3 DATA DERIVATIONS AND DEFINITIONS

General derivations that can be applied to any endpoint are defined below. For specific derivations that can only be applied to a particular endpoint, they will be defined in the section describing the endpoint.

Baseline Definition

Baseline measurement is defined as the last pre-treatment measurement obtained prior to the initial administration of BVD-523.

Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-procedure values. If either the baseline or post-procedure value is missing, the change from baseline is set to missing as well.

8 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed on the Safety Population.

8.1 SUBJECT DISPOSITION

The frequency and percentage of patients who receive at least one dose of BVD-523 or not, patients who have completed the study as per protocol or not, and patients who withdrew prematurely from the study with their reasons for discontinuation will be summarized by treatment group and overall (all treatment groups combined) for each study part[2]. The total number of mITT patients in each treatment group for each study part will be used as the denominator for the calculation of percentages.

The number and percentage of patients in each of the five analysis populations as specified in Section 5 will also be tabulated similarly.

A listing of analysis population, study completion, and early termination with the primary reason for early withdrawal will also be provided.

8.2 DEMOGRAPHIC CHARACTERISTICS

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall for each study part using the mITT and Safety Populations.

Demographic and baseline characteristics include, but are not limited to: age (years), age category (<65 and ≥65 years old), gender, ethnicity, race, weight (kg), height (cm), body mass index (BMI; kg/m^2), Eastern Cooperative Oncology Group (ECOG) Performance Score, reproductive status, cancer type, tumor mutation status, type of scan (Echocardiogram or Multi-gated acquisition scan (MUGA)), left ventricular ejection fraction (LVEF) result, and molecular abnormalities when available.
Age will be calculated in years from date of birth to the date of informed consent as an integer value. BMI is calculated as weight / $(height/100)^2$, where weight is in kg and height is in cm.

2 Part 1 and Part 2 use different categories. Part 1 categories are: Death, Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress), Withdrawal of Informed Consent, Disease Progression, Unacceptable Toxicity, Change in the Subject's Condition that Renders the Subject Unacceptable for Further Treatment, At Least 3 Interruptions of BVD-523 Intake, Patient Becomes Pregnant, Patient is Lost to Follow-up, Other. Part 2 categories are: 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, Other.

8.3 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO Drug, March 1, 2013). Summary of all medications will then be using the WHO Drug ATC classification and preferred term.

All medications taken, except for BVD-523, will be classified into prior or concomitant medications. A prior medication is defined as any medication taken within 28 days prior to the initiation of BVD-523 irrespective of whether it is continued into the study. A concomitant medication is defined as any medication taken after the initiation of BVD-523 and up to 30 calendar days after the last administration of BVD-523. If a medication falls into both prior and concomitant time phase then it will be presented in both time phases. All medications, except for BVD-523, will be summarized by WHO Drug ATC classification and preferred term with regards to treatment groups for each study part and time phase.

At each level (WHO Drug ATC classification and Preferred Term) of summarization, a subject will be counted only once per drug class or preferred term. For example, if a subject reports multiple concomitant medications with the same drug class, then that drug class will only be incremented by one. Similarly, if a subject reports multiple concomitant medications with the same preferred term, then that preferred term will only be incremented by one. Whether medications are taken for AEs or not will also be provided. The medication with indication equals to the AE verbatim which also has "Concomitant Medications" as the response to the question of "Any Treatment Required?" will be deemed as the medication taken for the AE. Medications taken for AEs will be tabulated by WHO Drug ATC classification and preferred term with regards to treatment groups for each study part.

Subject listing of medications will also be presented by time phase.

8.4 MEDICAL HISTORY

Medical history findings including change in medical condition since the last visit will be provided in a listing.

8.4.1 Previous Chemotherapy

Previous chemotherapy information includes description of the chemotherapy, start/stop date, reason for therapy, best response from the therapy, total number of cycles completed, prior anthracycline use, prior XRT use, and delivery site. They will be summarized by descriptive statistics by treatment group for each study part. Listing of previous chemotherapy information will also be provided in the order of occurrences within a patient.

8.4.2 Previous Immunotherapy

Previous immunotherapy data including type of immunotherapy (monoclonal antibodies, cancer vaccine, other immunotherapy), start/stop date, and reason for discontinuation (completed regimen, disease progression, other) will be listed by time of occurrence within a patient.

8.5 ON STUDY PROCEDURES

A listing of on study procedures including their purposes (prior medical condition, adverse event, other) will be provided.

8.6 INCLUSION/EXCLUSION CRITERIA

Inclusion and exclusion criteria failures will be included in a data listing.

8.7 TREATMENT COMPLIANCE

Patients will take BVD-523 orally twice daily for 21-day cycles until disease progression, unacceptable toxicity, or a clinical observation satisfying another withdrawal criterion is noted. Patients may be treated beyond disease progression for additional 21-day cycles at the Investigators 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. Treatment cycles will occur consecutively without interruption, except when necessary to manage toxicities. No intra-patient dose escalation was permitted under the original protocol or the first two amendments. Under amendment three, some intra-patient dose escalations were allowed. Under amendment four, intra-patient dose escalations are only allowed to bring subjects to the RP2D (after it is identified), if deemed medically appropriate and if the subject has not experienced any toxicity greater than Grade 1. Some intra-patient dose escalation may occur.
A listing of BVD-523 administration, dispensed, missed/interrupted dose, intra-patient dose escalations, returned, and compliance will also be provided.

8.8 PROTOCOL DEVIATIONS

Protocol deviations in the following areas will be collected from the study:

- drug dosing,
- exclusion criteria,
- general protocol issues,
- informed consent form issues,
- inclusion criteria,
- missed study procedure,
- SAE issues,
- visit windows,
- other, and
- unknown.

Impacts of the above protocol deviations on the analysis population will be determined by study team before study closure and documented in the SAP.
The frequency and percentage of patients with each protocol deviation along with the impact on the analysis population will be presented by treatment group and overall for each study part using the ITT Population. A listing of patients with protocol deviation(s) will also be provided.

9 EFFICACY ANALYSIS

Unless otherwise stated, efficacy analyses will be performed on both the mITT and PP populations (see Section 5 of this SAP).

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 first protocol-specified tumor measurement evaluation at the end of Cycle 2 and then every 2-3 cycles, and at End of Treatment.

In Part 1, FDG-PET scans were performed at investigator discretion based on totality of additional available data for the subject.

RECIST
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 in evaluation of target lesions 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.

The number and percent of patients with each tumor response will be tabulated using the PP Population by study part, dose level/treatment group, and study visit. Bar graphs of genetic information (BRAF, FGFR3, etc.) leading to target lesion response and best overall response will also be presented.

10 SAFETY

Safety analyses will be performed using the Safety Population. Safety will be assessed by examining all adverse events reported during the study including the incidence, and relationship to BVD-523. In addition, safety evaluations will be conducted at Screening, Baseline, 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, ECOG performance status, vital signs, and clinical laboratory evaluations (hematology,

chemistry, urinalysis and pregnancy test). Electrocardiography measurements will be collected in Cycle 1 (determined by ECG at Screening and Day 8 and 12±2 hours Holter monitoring during PK sampling days). Patients with a normal ECG in Cycle 1 need not have repeat ECGs in subsequent cycles. An ophthalmologic assessment will also be conducted at screening, at the end of study and at other visits by an ophthalmologist if clinically indicated. Additionally, subjects will be asked to return for a 30 day safety visit (or earlier if subsequent therapy is initiated prior to 30 days) or contacted by phone after the last dose of study medication is taken.

10.1 EXPOSURE TO STUDY DRUG

Descriptive statistics will be provided for the total (cumulative) doses taken and total duration of treatment by treatment group for each study part. The total duration of treatment is calculated as (treatment stop date – treatment start date) + 1. If treatment stop date is missing, the date of final clinic visit will be used. By subject listing of study drug exposure will also be presented by study part and treatment group for each treatment cycle and all cycles combined.

10.2 ADVERSE EVENTS

An adverse event 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. This includes an exacerbation of pre-existing conditions or events, inter-current illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. The reporting period of an AE begins from the time that the patient provides informed consent through and including 30 calendar days after the last administration of BVD-523 (or at the time when a patient begins a new anti-cancer therapy). 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.

The severity of an AE will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4 with values of Grade 1 to Grade 5 (increased in severity). For AEs not covered by NCI CTCAE, the severity will be characterized as “mild,” “moderate,” or “severe” according to the following definitions:

- Mild (equivalent to Grade 1) events are usually transient and do not interfere with the patient’s daily activities.
- Moderate (equivalent to Grade 2) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe (equivalent to Grade 3) events interrupt the patient’s usual daily activities.

All AE relationship to the study drug, BVD-523, are classified as “unrelated,” “possibly related,” or “related.”

AE Coding

Any AE including SAE in verbatim term will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary version 16.0 to a system organ class (SOC) and preferred term (PT) within each SOC. Analysis of AEs will then be performed using SOCs and PTs.

Dose Limiting Toxicities, Maximum Tolerated Dose, and Recommended Phase 2 Dose

As specified in Section 2.1.1, a DLT for Part 2 is defined (per definition in protocol amendment 7) as a **BVD-523 related toxicity** in the first 21 days of treatment that results in:

- ≥ Grade 4 hematologic toxicity for > 1 day;
- Grade 3 hematologic toxicity with complications e.g., thrombocytopenia with bleeding;
- ≥ 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].

As specified in Section 2.1.1, the MTD is defined as the highest dose level at which ≤33% of patients experience BVD-523 related DLTs in the first 21 days of treatment. The 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 (PK), pharmacodynamics (PD), and any cumulative toxicity observed after multiple cycles may be included in the rationale supporting the RP2D. Pharmacokinetic, pharmacodynamics, and/or Holter measurements may be suspended pending review of accumulated patient experience.

Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is any AE temporally associated with the use of BVD-523 (from BVD-523 initiation until 30 calendar days after the last administration of BVD-523), whether or not considered related to the study drug. If the onset of an AE is missing and the AE resolution date is either after the initial BVD-523 dose date or missing, then the AE will be considered treatment emergent.

AE Summaries

A subject who reported multiple AEs that map to a common PT or SOC is counted only once for that PT or SOC at the highest severity reported and at the greatest relationship to study drug.

The number and percentage of subjects who experienced at least one AE will be tabulated by SOC and PT with respect to dose level/treatment group for each study part. The same tabulation will also be applied to any SAE, any AE leading to premature discontinuation from the study, treatment emergent AEs and treatment-emergent SAEs.

[3] For Amendments 1 and 2: A treatment interruption exceeding 3 days in Cycle 1 due to drug-related toxicity (or inability to begin Cycle 2 for > 7 days) due to drug-related toxicity.

For Amendment 3: A treatment interruption exceeding 5 days in Cycle 1 due to drug-related toxicity (or inability to begin Cycle 2 for > 7 days due to drug-related AE)

For Amendments 4, 5, and 6: 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.

The number and percentage of subjects who experienced at least one AE will also be tabulated by SOC and PT within each dose level/treatment group with respect to relationship to study drug (unrelated, possibly related, and related) and severity (Grade 1 to Grade 5). Subject listings will also be provided for all AEs, all SAEs, all AEs leading to early discontinuation from the study and all AEs leading to study drug interruptions and length of interruptions.

Bar graphs of AEs in CTCAE Term will be displayed in decreasing order of incidence from most common to least common. Each bar in the plot will represent an AE in CTCAE Term. Severity of AE (grades) will be embedded in each bar using the percentages of patients in each AE grade. These plots will be provided for all AE tables produced.

10.3 SERIOUS ADVERSE EVENTS AND DEATH

Separate data listings and summaries will be presented for all SAEs and deaths.

10.4 LABORATORY EVALUATIONS

Laboratory evaluations obtained from the following clinical laboratory tests will be collected at Screening, Baseline, Days 8, 15, 22, 29, 36, 43, and, in patients who continue treatment, every 3 weeks or if clinically indicated thereafter:

- **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, creatinine clearance, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), Lactic dehydrogenase (LDH), sodium, blood urea nitrogen (BUN), and 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 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.

Results of all evaluations (normal, abnormal clinically significant, abnormal not clinically significant, not done) from each laboratory test will be tabulated by study visit and treatment group for each study part. A listing of all laboratory evaluations and abnormal clinically significant laboratory evaluations will also be provided.

10.5 VITAL SIGNS

Descriptive statistics for systolic blood pressure (mm Hg) diastolic blood pressure (mm Hg), pulse rate (bpm), temperature (°C), height (cm), and weight (kg) will be presented by study visit and treatment group visit for each study part. Also, changes in these vital signs from baseline to each subsequent visit will be tabulated by dose level/treatment group for each study part. Note that height is only collected at Screening and weight is only collected at Screening and at the beginning of each cycle of treatment.

A listing of vital signs will also be provided.

10.6 ELECTROCARDIOGRAMS AND HOLTER MONITORING

Electrocardiogram (ECG) readings and Holter Monitoring are assessed by BioClinica (Princeton, NJ). All patients will have Screening and Cycle 1 (at Day 8) ECG evaluated to have ECG parameters (Heart Rate (bpm), RR (msec), PR (msec), QRS (msec), QT (msec), and QTcF (msec)) collected. The QT data will be corrected using Fridericia correction and calculated as $QTcF = QT/[RR^{(1/3)}]$. Furthermore, an overall assessment of the ECG results on a subject-visit level will be classified as 'Normal', 'Abnormal, Not Clinically Significant', or 'Abnormal, Clinically Significant'.

During PK sampling days (Cycle 1, Day 1 and 15), a subset of patients will have Holter monitoring (12± 2 hours) performed.

For subjects with a clinically significant abnormal ECG in Cycle 1, their ECGs will be conducted at Days 22, 29, 36, 43, and, in patients who continue treatment, every 3 weeks or if clinically indicated thereafter.

Holter ECG analyses will be conducted by BioClinica and are detailed in the Clinipace Worldwide/BioClinica work order. All ECG parameters will be summarized as actual values and as changes from screening/baseline by study visit AND treatment group for each study part; assessments by cohort will only be performed for cohorts of at least 3 subjects.

The primary analysis will be a concentration-response (PK:PD) analysis of QTcF, assuming no hysteresis and a linear relationship between PK and QTc. Secondary analyses will provide summary statistics by time-point and dose for: HR, PR, QRS, QT, and QTcF.

A listing of ECG findings will also be provided.

10.7 OPHTHALMOLOGY EXAMINATIONS

Ophthalmologic examinations findings include best-corrected visual acuity, visual field examination, intraocular pressure, external eye examination, and dilated fundoscopy will be collected at Screening, at study termination, and if clinically indicated.

Descriptive statistics will be used to summarize these ophthalmologic examinations findings. A listing of all ophthalmologic examinations findings will also be provided

10.8 PHYSICAL EXAMINATIONS

Physical examinations will include examination of general appearance; skin; eyes; ears, nose, & throat; head & neck; heart; chest & lungs; abdomen; extremities; back; lymph nodes; musculoskeletal; and neurological. These examinations will be conducted at Screening, Baseline, Days 8, 15, 22, 29, 36, 43, and, in patients who continue treatment, every 3 weeks or if clinically indicated thereafter.

The frequency and percentage of patients with each examination finding ('Normal', 'Abnormal Clinically Significant', 'Abnormal Not Clinically Significant', and 'Not Done') will be tabulated for each body system by study visit and dose level/treatment group for each study part.

A listing of physical examination findings will be presented.

11 ADDITIONAL ANALYSES

11.1 PHARMACOKINETIC ANALYSES

Samples for PK analysis of BVD-523 and selected metabolites will be obtained from all Part 1 patients during their first cycle of treatment (Cycle 1). PK samples may also be obtained from additional patients in Part 2 depending on the outcome of initial PK analysis.

At Visit 2 (Baseline) blood samples (3 mL) will be collected prior to dosing, and then at 0.5, 1 (±5 minutes), 2, 4, 6, 8 (±10 minutes), and 12 (± 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, 2, 4, 6, 8, and 12 ± 2 hours post-dose. A single sample will be collected on Day 22 prior to dosing on that day.

For Part 1 subjects, at Visit 2 (Baseline) urine samples will be collected pre-dose. Total urine for the 1–6-hour and 6–12 ±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 for the 1–6-hour and 6–12 ±2-hour time periods post-dose. No urine PK samples will be collected for Part 2 subjects.

Below is the list of various PK parameters that will be calculated after Dose 1 (Day 1) and at Steady State (Day 15) using both blood and urine samples:

PK Parameter (plasma)	Description
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 postdose, calculated by linear/log trapezoidal method
AUC_{1-12}	Area under the plasma concentration-time curve from 1 to 12 hours postdose, 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

λ_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 λ_z
$t_{1/2}$	Terminal half-life, defined as 0.693 (ln 2) divided by λ_z

PK Parameter (urine)	Description
U_{1-6}	Amount excreted in urine calculated from Time 1 to 6 hours
U_{1-12}	Cumulative 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.

Only AUC_{0-last} will be calculated from the single sample collected at prior to dosing on Day 22.
PK concentration and PK parameters calculated from both blood and urine samples will be provided by Covance. Descriptive statistics [n, arithmetic mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric standard deviation geometric CV]will be used to summarize PK parameters by treatment. For $t_{1/2}$ and t_{max}, regular descriptive statistics and 95% confidence intervals about the arithmetic mean will be calculated, if possible, for each dose, but not geometric mean, geometric standard deviation, and geometric CV. Refer to Pharmacokinetic Analysis Outline (PKAO) for additional details re. the PK analyses.

Listings of PK concentrations (blood and urine) and PK parameters will also be provided.

11.2 PHARMACODYNAMICS ANALYSES

Multiple biomarkers intended to demonstrate inhibition of the molecular target, and mechanism of action will be investigated (pRSK, pERK, Ki67, Caspase-3, and circulating tumor DNA) from fluid and tissue samples. Additional biomarkers may be identified and measured as appropriate. 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 sample taken. Descriptive statistics will be provided for pharmacodynamics data collected from fluid samples. Listings of pharmacodynamics data will be provided from both fluid and tissue samples.

11.3 TUMOR GENOTYPING

Tumor genotyping by DNA analysis may be performed in patients in Part 1. For patients enrolled in Part 2 tumor genetic information (detected mutation) will be required to confirm eligibility. When available the predicted mutation and/or protein change will also be collected.

Descriptive statistics and listing of tumor genotyping data will be provided.

12 INTERIM ANALYSIS

Once all subjects enrolled into Part 1 of the study have been assessed for at least one full treatment cycle, an analysis of Part 1 safety and efficacy will be conducted in order to facilitate the discussions regarding MTD and RP2D; however, no formal interim analysis is planned for the study.

13 END-OF-STUDY-ANALYSIS

A final analysis will be conducted after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

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Part I – Listing 16.2.5.3 Electrocardiograms

Part I – Listing 16.2.5.4 Holter Monitoring

Part I – Listing 16.2.5.5 Holter Monitoring Finding

Part I – Listing 16.2.5.6 Ophthalmology Examinations

Part I – Listing 16.2.5.7 Vital Signs

Part I – Listing 16.2.5.8 Pregnancy Results

Pharmacokinetics

Part I – Listing 16.2.6.1 Pharmacokinetic Concentration Measured from Blood Samples

Part I – Listing 16.2.6.2 Pharmacokinetic Concentration Measured from Urine Samples

Part I – Listing 16.2.6.3 Pharmacokinetic Parameters

Pharmacodynamics

Part I – Listing 16.2.7.1 Fluid/Blood Pharmacodynamics

Part I – Listing 16.2.7.2 Tissue Pharmacodynamics

Tumor Genotyping

Part I – Listing 16.2.8 Tumor Genetic or Genotyping Information / Result

Part II

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Part II – Listing 16.2.1.1 Subject Disposition

Part II – Listing 16.2.1.2.1 Protocol Deviations

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Part II – Listing 16.2.1.4 Medical History

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Part II – Listing 16.2.1.6 Previous Chemotherapy

Part II – Listing 16.2.1.7 Previous Immunotherapy

Part II – Listing 16.2.1.8.1 Relationship of WHO Drug ATC Classification and Preferred Term with Verbatim

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Part II – Listing 16.2.3.1 RP2D from Part I

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Part II – Listing 16.2.5.7 Vital Signs
Part II – Listing 16.2.5.8 Pregnancy Results

Pharmacokinetics

Part II – Listing 16.2.6.1 Pharmacokinetic Concentration Measured from Blood Samples
Part II – Listing 16.2.6.2 Pharmacokinetic Parameters

Pharmacodynamics

Part II – Listing 16.2.7.1 Fluid/Blood Pharmacodynamics
Part II – Listing 16.2.7.2 Tissue Pharmacodynamics

Tumor Genotyping

Part II – Listing 16.2.8 Tumor Genetic Information

15 REVISIONS TO SAP

The SAP dated 10MAR2015 was finalized/signed for Part 1, under protocol amendment 4. This version of the SAP has been revised to reflect changes to the protocol in amendments 5, 6, and 7; and to update the list of TFL shells for Part 2.

The definition of mITT used in the SAP (see Section 5.2) is slightly different from the protocol. The protocol defined the mITT population as all subjects who sign informed consent, which would result in the inclusion of screen failure subjects in the mITT population. To avoid this, the SAP modified the mITT definition to be all enrolled subjects, thereby excluding screen failures.

16 REFERENCES

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NCI CTCAE Grading Scale Version 4 (see the NCI CTCAE web page at http://ctep.cancer.gov for details).