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

Abbreviation	Definition
AE	Adverse Event
AML	Acute Myelogenous Leukemia
AMS	Acute Myelodysplastic Syndrome
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutic Chemical
BM	Bone Marrow
BID	Twice Daily
CFB	Change from Baseline
CML	Chronic Myeloid Leukemia
CMML	Chronic Myelomonocytic Leukemia
CPWW	Clinipace Worldwide
CR	Complete Remission
CRF	Case Report Form
CRi	Complete Response with incomplete blood count recovery
CRp	Complete Response with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
ITT	Intent-to-Treat
Max	Maximum
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase/extracellular signal-related kinase
Min	Minimum
MTD	Maximum Tolerated Dose
MUGA	Multi-gated Acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria AE Severity
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Remission
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK), and preliminary efficacy data from Protocol BVD-523-02. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

2 STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary Objectives

The primary objectives of the study are:

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

2.1.2 Secondary Objectives

Secondary objectives of this study are:

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

2.1.3 Exploratory Objectives

- To evaluate pharmacodynamic marker (biomarker) measures.

2.2 TREATMENT GROUPS

This Phase 1/2 study is single-arm.

In Phase 1 (Dose Escalation) the treatment group is subjects treated with orally administered BVD-523 BID.

In Phase 2 (Cohort Expansion) the treatment group is subjects treated with orally administered BVD-523 BID at the RP2D in one of two groups: RAS mutant positive or RAS mutant negative.

2.3 STUDY ENDPOINTS

2.3.1 Primary Endpoint

The primary safety endpoints are the DLTs and MTD for BVD-523 administered alone in subjects with AML or MDS (Part 1) and the MTD for BVD-523 administered at the RP2D dose in subjects with AML or MDS with or without RAS mutant positive disease (Part 2).

As this is a Phase 1/2 study, there is no formal primary efficacy endpoint; however, clinical response will be assessed.

2.3.2 Secondary Endpoints

Secondary endpoints are:

- Pharmacokinetic (PK) profile of BVD-523 and selected metabolites
- Progression Free Survival (PFS) and Duration of Response (DOR) in subjects achieving Complete Response (CR) or Complete Response with incomplete platelet response (CRp)

2.3.3 Exploratory Endpoints

- Pharmacodynamic markers (biomarker)

3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This study is an open label, Phase 1/2 clinical trial in subjects with AML or MDS. The trial has a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2).

Part 1 – Dose-escalation Phase: The dose-escalation phase is a 3+3 design to determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (R2PD) of BVD-523 given twice-daily. The starting dose of BVD-523 will be 300 mg BID. Treatment will be administered in continuous, sequential 21 day Cycles until disease progression, unacceptable toxicity, or another withdrawal condition is met. Dose-escalation decisions will be based on Cycle 1 data. Within-subject dose escalations are allowed after completing one Cycle at the initial dose, pending complete Cycle 1 data for the dose to be escalated to. The MTD will be determined based on the highest dose associated with no more than 1 DLT in fewer than 6 subjects. Cohorts will be based on 3 subjects, but can be enlarged as deemed necessary by the Safety Monitoring Committee. Once a dose associated with more than 1 DLT in fewer than 6 subjects has been identified, intermediate doses may be examined to obtain a better estimate of the MTD.

Part 2 – Cohort-expansion Phase: Approximately 40 additional subjects will be recruited to one of two groups:

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

Subjects in both groups will receive treatment at the Recommended Phase 2 Dose (RP2D). Subjects will receive twice daily oral doses of BVD-523 in 21-day treatment cycles until disease progression, unacceptable toxicity, or another withdrawal criterion is met. Treatment cycles will occur consecutively without interruption except when necessary to manage adverse events.

DLTs

For this study, Dose Limiting Toxicities (DLTs) are based upon the first Cycle (first 21 days of treatment), defined as (where Grade refers to CTCAE v 4.0 categorization):

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

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

Dose escalation will proceed according to the following rules:

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

MTD

The Maximum Tolerated Dose (MTD) will be determined based on the highest dose cohort at which <33% of subjects experience BVD-523 related DLTs in the first 21 days of treatment.

Once a non-tolerated dose has been identified, intermediate doses may be examined to obtain a better estimate of the MTD.

RP2D

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

3.2 SCHEDULE OF STUDY ASSESSMENTS

Table 3.1 Part 1 and 2: Schedule of Assessments and Procedures

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

Table 3.1 Part 1 and 2: Schedule of Assessments and Procedures

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

Table footnotes:

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

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

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

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

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

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

g Pharmacodynamic, PK and PBMC blood samples are required at baseline where feasible. Additional biomarkers and DNA sequence analysis may be identified and measured as appropriate by collection of whole blood prior to dosing initiation and after drug levels have reached steady-state. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patients are not at steady state, these assessments will be rescheduled and completed at the next visit in which steady state is achieved. Leukemic cell genotyping by DNA analysis may be performed to identify somatic alterations, relying on either available stored samples or freshly collected samples.

h Bone marrow aspirate and/or biopsy. Peripheral, Geimsa and Iron stained slides to be provided with each bone marrow aspirate or biopsy. Bone marrow aspirate and/or biopsy slides will not be shipped to a third party. As such, the site may utilize BM aspirates performed in clinical practice as SOC, as long as they are collected within the screening window (-28 days). Bone marrow cytogenetics (cytogenetics should include at least 20 clones). Bone marrow aspirates may be used to evaluate biomarkers of drug response.

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

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

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

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

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

Table 3.2 Pharmacokinetic Parameters to be Estimated after Dose 1 and at Steady State

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

Table 3.3 Study Medication Dosing and Pharmacokinetics/Pharmacodynamics Chart

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

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

4 SAMPLE SIZE CONSIDERATIONS

The expected sample size is 60 subjects: 20 in Part 1 and 40 in Part 2 (20 subjects each in RAS mutant positive and RAS mutant negative groups). This sample size was selected based on the sample size for similar Phase 1 oncology clinical trials.

5 ANALYSIS POPULATIONS

The following population definitions will be used in study summaries and analyses.

5.1 SCREENED

The Screened Population will consist of all patients who have signed the informed consent. The screened population will be used for disposition tables.

5.2 SAFETY

The Safety Population will consist of all subjects receiving at least 1 dose of study drug. Demographic and baseline characteristics will be tabulated for the Safety population. The Safety population will be used for all safety analyses. Safety analyses from Part 1 will be presented overall as well as broken down by dose level. Safety analyses from Part 2 will be presented overall as well as broken down by dose level, specifically at the RP2D dose of 600 mg.

5.3 MODIFIED INTENT-TO-TREAT

The modified Intent-to-Treat (mITT) Population will consist of all subjects who have a screening visit / sign the informed consent and had no screening failures/were eligible for treatment regardless of whether or not they have received treatment. Demographic and baseline characteristics will be tabulated for the mITT population. Additionally, the mITT population will be used for calculating response in Part 2.

5.4 PER PROTOCOL

The Per Protocol (PP) Population will consist of all subjects in the mITT population who receive at least 1 dose of study drug, complete the first protocol-specified tumor measurement evaluation (except for study drug-related AE), and complete the study without a major protocol deviation (see Section 8.6). Demographic and baseline characteristics will be tabulated for the PP population. Additionally, the PP population will be used for calculating MTDs in Part 1 and response in Part 2.

5.5 PHARMACOKINETIC

The PK population will consist of all subjects who receive at least 1 dose of study drug and have sufficient, valid PK samples to estimate key parameters for at least 1 of the days of sampling. PK summaries will be based on the PK population.

5.6 PHARMACODYNAMIC

The PD population will consist of all subjects who receive at least 1 dose of study drug and have sufficient, valid PD samples to estimate key parameters for at least 1 of the days of sampling. PD summaries will be based on the PD 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

No covariates will be accounted for in Part 1. In Part 2, analyses will be conducted separately by RAS mutation status (positive or negative).

6.3 SUBGROUPS

There are no planned subgroup analyses.

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 with a significance level (α) of 0.05 and utilize two-sided testing.

6.6 STATISTICAL NOTATION AND METHODOLOGY

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (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 rounded to 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 (zeroes are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries. P-values will be presented with 3 decimal places and values less than 0.001 will be presented as < 0.001.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by study part (Part 1 or Part 2), subject number, and then by date/time for each subject number. For Part 2, subjects will additionally be sorted by RAS mutation status.

7 DATA HANDLING METHODS

7.1 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, the 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.

Study visit periods will be windowed as applicable according to the following:

Visit	Nominal Study Day	Study Day Window
Screening		-28 to -1
Baseline (pre-dose and post-single dose)	1	N/A (Other visits are scheduled based on this visit)
Cycle 1		
Day 8	8	7 to 9
Day 15	15	14 to 16
Cycle 2		
Day 1	22	21 to 23
Day 8	29	28 to 30
Day 15	36	35 to 37
Cycles 3-X		
Day 1	21*X + 1	-1 to +1

Values will be presented for all scheduled study visits according to the nominal visit obtained from the CRF. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. If no nominal visit assessment exists for a visit window with unscheduled visit(s), then the latest unscheduled visit

within the visit window will be used. If multiple nominal assessments are collected within the same visit, the latest value and corresponding date will be used for summary presentation.

All values will be included in the data listings.

7.2 DATA DERIVATIONS AND DEFINITIONS

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.

Study days on or after the initial dose of BVD-523 will be computed as Study Day = Date – Study Drug Start Date + 1. For pre-dosing dates, Study Day = Date – Study Drug Start Date.

Age will be calculated from the date of birth to informed consent visit date. Note, that if multiple dates occur for the screening visit, the convention as described at the end of Section 7.3.1 will be used.

Treatment-emergent events will be considered as any event occurring after the first dose of study drug and prior to a subject's termination, withdrawal, or completion of the study.

The following will define prior medication use versus concomitant medication use:

- Prior use ended before the first day of study drug
- Concomitant use is on or after the first day of study drug (initiation date, stop date).

7.3 MISSING DATA

7.3.1 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.

7.3.2 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."

8 STUDY POPULATION

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

8.1 SUBJECT DISPOSITION

Subject disposition will be presented for all subjects. The composition of the analysis populations and those who were screen fails, enrolled, completed or discontinued from the study will be summarized by dose cohort and overall with descriptive statistics. Reasons for early discontinuation will be presented with frequencies and percentages for all categories.

The frequency and percentage of subjects who are screen fails, subjects who receive at least one dose of BVD-523 or not, subjects who have completed the study as per protocol or not, and subjects who withdrew prematurely from the study with their reasons for discontinuation (death, anaphylaxis, withdrawal of informed consent, disease progression, unacceptable toxicity, change in the subject's condition that renders the subject unacceptable for further treatment in the special treatment of PI, at least 3 interruptions of BVD-523 intake of >7 days each, or 8 consecutive days, subject becomes pregnant, subject is lost to follow-up, or other) will be summarized by treatment group and overall (all treatment groups combined) separately for Study Parts 1 and 2. The total number of mITT subjects in each treatment group for each study part will be used as the denominator for the calculation of percentages.

The number and percentage of subjects in each of the 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 AND BASELINE CHARACTERISTICS

Demographic and baseline characteristic data will be summarized with descriptive statistics for (including but not limited to): age, gender, race, AML or MDS subtype (including relapsed or refractory status), bone marrow molecular cytogenetics, RAS positive or negative status (optional for Part 1, required for Part 2), body weight and height, ECOG performance status, previous chemotherapy, and previous immunotherapy.

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

Demographic and baseline characteristics include, but are not limited to: age (years), gender, ethnicity, race, weight (kg), height (cm), Eastern Cooperative Oncology Group (ECOG) Performance Score, cancer type (AML or MDS), bone marrow cytogenetics, RAS mutation status, previous chemotherapy and previous immunotherapy. Age will be calculated in years from date of birth to the date of informed consent as an integer value.

8.3 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO Drug, March 2015). A summary of all medications will then be provided 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 will be summarized with descriptive statistics by medical history code. A comprehensive data listing will also be included. Specific intervention of interest include prior cancer surgery related to AML or MDS, chemotherapy, immunotherapy, hormonal, radiation, stem cell treatment and MEK therapies.

8.4.1 Prior Cancer Surgery Related to AML or MDS

Prior cancer surgeries related to AML or MDS will be summarized by indication (diagnostic, therapeutic, or other) and time prior to enrollment into the trial. They will be summarized by descriptive statistics for each study part. A listing will also be provided in the order of occurrences within a subject.

8.4.2 Previous Chemotherapy

Previous chemotherapy information includes description/name of the chemotherapy, start/stop date, reason for therapy, best response from the therapy, total number of cycles completed, best

response, and reason for discontinuation. They will be summarized by descriptive statistics for each study part. A listing of previous chemotherapy information will also be provided in the order of occurrences within a subject.

8.4.3 Previous Immunotherapy

Previous immunotherapy data including type of immunotherapy/name (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 subject.

8.4.4 Previous Hormonal Therapy

Previous hormonal therapy including type, start/stop date, reason for therapy, best response for therapy, total number of cycles completed, and reason for discontinuation (completed regimen, disease progression, other) will be listed by time of occurrence within a subject.

8.4.5 Previous Radiation Therapy

Previous radiation therapy including type, total dose, delivery site, start/stop date, reason for therapy, best response for therapy, total number of cycles completed, and reason for discontinuation (completed regimen, disease progression, other) will be listed by time of occurrence within a subject.

8.4.6 Previous Stem Cell Therapy

Previous stem cell therapy including type, start/stop date, reason for therapy, best response for therapy, total number of cycles completed, and reason for discontinuation (completed regimen, disease progression, other) will be listed by time of occurrence within a subject.

8.4.7 Previous Transfusion/Blood Product Use

Previous transfusion/blood product use blood product, date, amount transfused, and relevant test results (e.g. hemoglobin, platelets, or other) will be listed by time of occurrence within a subject.

8.4.8 Prior MEK Therapies

Prior MEK therapies including type, start/stop date, duration (days), reason for therapy, best response for therapy and reason for discontinuation (completed regimen, disease progression, other) will be listed by time of occurrence within a subject.

8.5 INCLUSION/EXCLUSION CRITERIA

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

8.6 PROTOCOL DEVIATIONS

Protocol deviations will be summarized with descriptive statistics by cohort and category. All protocol deviations will be reported, but prior to generating Part 1 TFLs or Part 2 TFLs the list of protocol deviations will be reviewed and each classified as either major or minor. A listing of all events will also be included. Protocol deviation categories are:

- Inclusion/exclusion criteria
- Informed consent issue
- Out of window visit
- Protocol required evaluation not completed
- Physician decision
- Subject refused
- Prohibited medication
- Pharmacokinetic data
- Other

Impacts of the above protocol deviations on the analysis population will be determined by the study team before study closure and documented in the SAP.

The frequency and percentage of subjects 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 mITT Population. A listing of subjects with protocol deviation(s) will also be provided.

9 EFFICACY ANALYSIS

Unless otherwise stated, efficacy analyses will be performed on both the modified ITT and PP populations.

9.1 PRIMARY ENDPOINT ANALYSIS

As this is a Phase 1/2 study, there is no formal primary efficacy endpoint.

The primary safety endpoints are the DLTs and MTD for BVD-523 administered alone in subjects with AML or MDS (Part 1) and preliminary efficacy (AML/MDS response) of BVD-523 administered at the RP2D dose in subjects with AML or MDS with or without RAS mutant positive disease (Part 2). The MTD and RP2D will be determined based upon the observed DLTs at each dose level as described in the protocol.

9.2 SECONDARY ENDPOINT ANALYSES

While no formal efficacy analyses will be conducted, secondary efficacy endpoints are:

- Pharmacokinetic (PK) profile of BVD-523 and selected metabolites
- Progression Free Survival (PFS) and Duration of Response (DOR) in subjects achieving Complete Response (CR) or Complete Response with incomplete platelet response (CRp)

9.2.1 PK profile

Pharmacokinetic analyses are discussed in Section 11 of this SAP.

9.2.2 Response

Subject response will be determined differently depending on disease type (MDS or AML).

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

Table 9.1 Table 3 from IWG 2006 MDS Response Criteria

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

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

**Added as a response option in Note to File dated 21JUL2015.

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

Table 9.2 Table 4 from IWG 2003 AML Response Criteria

Response	Peripheral Blood	Bone Marrow
Complete Remission (CR)	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L, independence from red cell and platelet transfusions over the past week	≤ 5% blasts
Complete Remission with Incomplete Platelet Recovery (CRp)	ANC > 1.0 x 10^9/L, Platelets < 100 x 10^9/L, independence from red cell transfusions over the past week	≤ 5% blasts
Complete Response with Incomplete Blood Count Recovery (Cri)	ANC < 1.0 x 10^9/L	≤ 5% blasts
Partial Remission (PR)	ANC > 1.0 x 10^9/L, Platelets ≥ 100 x 10^9/L	Decrease of ≥ 50% in blasts to level of 5% to 25%
Less than Partial Remission*		

ANC = absolute neutrophil count

*Added as a response option in Note to File dated 21JUL2015

9.3 OTHER EFFICACY ANALYSES

There are no other efficacy analyses.

9.4 INTERIM ANALYSIS

There will not be a formal interim analysis; however, TFLs will be generated for Part 1 after a MTD is determined; i.e. as Part 2 is ongoing.

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 Baseline, Days 1, 8, 15, 22, 29, 36, 43, and, in subjects who continue treatment, every 3 weeks or if clinically indicated thereafter. These evaluations will include a targeted ECG where clinically warranted, and clinical laboratory analytes (hematology, chemistry, urinalysis and pregnancy test). An ophthalmologic assessment will also be conducted at baseline, at the end of study and at other visits by an ophthalmologist if clinically indicated.

10.1 EXPOSURE TO STUDY DRUG

All exposure and compliance data will be provided in data listings.

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. Treatment compliance is accessed by reviewing pill count. Patient frequencies will be provided for the summary of treatment compliance.

10.2 ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a subject 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 subject provides informed consent through and including 30 calendar days after the last administration of BVD-523 (or at the time when a subject begins a new anticancer 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 4.03 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 events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject'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 17.1 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 3.1, a DLT is defined as a **BVD-523 related toxicity**[1] in the first 21 days of treatment that results in:

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

As specified in Section 3.1, the MTD is defined as the highest dose level at which no more than 1 of 6 subjects experiences 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.

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 as well as subjects who experienced at least one TEAE 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 treatment emergent SAEs and any TEAEs leading to premature discontinuation from the study as well as to any DLTs.

[1] All toxicities will be considered related to BVD-523 if they cannot be definitively explained by underlying disease, intercurrent illness or concomitant medications.

The number and percentage of subjects who experience at least one TEAE will also be tabulated by SOC and PT within each dose level treatment group with respect to relationship to study drug (unrelated and at least possibly related [combining events classified as either possibly related or related]) and severity (Grade 1 to Grade 5 and ≥Grade 3). The tabulation by relationship (unrelated and at least possibly related) will also be applied to any treatment emergent SAEs (TESAEs).

Subject listings will also be provided for all AEs, all SAEs, all AEs leading to early discontinuation from the study, 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 subjects in each AE grade. These plots will be provided for all AEs, TEAEs, treatment-emergent SAEs, and AEs leading to premature discontinuation from the study.

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 assessments and change from baseline will be summarized with descriptive statistics by panel, test, dose of BVD-523, and time point. Additionally, abnormal results will be summarized with frequencies and percentages by clinical significance, panel, test, treatment group, and time point. The clinical significance of lab tests will also be summarized by shift tables.

A data listing will display all laboratory test results and findings.

Laboratory evaluations obtained from the following clinical laboratory tests will be collected at Screening, Baseline, Days 8, 15, 22, 29, 36, 43, and, in subjects 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, and platelet count.
- **Blood Chemistry** – albumin, alkaline phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, blood urea nitrogen (BUN), uric acid, cholesterol and triglycerides (at screening and first day of Cycle 1).
  - If total bilirubin concentration is increased above 1.5 times the upper normal limit, total bilirubin should be differentiated into direct and indirect reacting bilirubin.
- **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.

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 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

Subjects will have ECG measured at Screening and on Cycle 1, Day 8. Subjects with normal ECGs do not need to have subsequent ECGs. ECG parameters [Heart Rate (bpm), RR (msec), PR (msec), QRS (msec), QT (msec), and QTcF (msec)] collected. These ECG findings will be summarized with frequencies and percentages by dose and time point. ECG results will also be categorized as 'Normal', 'Abnormal, Not Clinically Significant', or 'Abnormal, Clinically Significant' and any clinically significant abnormalities described.

10.7 PHYSICAL EXAMINATIONS

Full physical examinations at Screening will include examination of general appearance, skin, eyes, ears, nose, throat, head, neck, chest, lungs, heart, abdomen, back, lymph nodes, extremities, musculoskeletal, neurological examinations and other. Subsequent targeted physical exams should include body systems as appropriate.

The frequency and percentage of subjects 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 also be presented.

10.8 ECOG PERFORMANCE STATUS

The ECOG performance status is a rating scale used to assess how a subject's disease is progressing as well as how the disease affects the daily living abilities of the subject. The score values are 0 – 5, where 0 indicates "fully active, able to carry on all pre-disease performance without restriction" and 5 indicates the subject has died. It will be assessed at Screening, Baseline, Study Days 8, 15, 22, 29, 36, 43, and in subjects who continue treatment, every 3 weeks or if clinically indicated thereafter.

The frequencies and percentages of subjects' ECOG performance status will be provided by study visit and dose level treatment group for each study part. A listing of ECOG performance status will also be provided.

10.9 BONE MARROW ASSESSMENT

Bone marrow assessments (aspiration or biopsy, cytogenetics) will be collected at prior to therapy on Day 1 and Day 22, every 2 cycles thereafter, as well as at the Final Study Visit. Bone marrow aspirate/biopsy will be examined for: adequacy, fibrosis, cellularity, iron stores, ringed sideroblasts, histiocytes, dysplasia, bone marrow differential, and myeloid to erythroid ratio. Aspirate/biopsy samples will also be examined for biomarkers of drug response, e.g. pRSK and total RSK. Cytogenetics assessments will examine for common mutations.

11 PHARMACOKINETIC ANALYSES

Analyses of serum concentrations collected at Baseline (Visit 2, Cycle 1) and Day 22 (Visit 5, Cycle 1). Samples will be collected prior to administration of first daily dose and then post-dosing at 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours.

Descriptive statistics will be used to summarize concentration assessments and estimated PK parameters by treatment group and time point. Comprehensive data listings will also be included.

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

At Visit 2 (Baseline) blood samples will be collected prior to dosing, and then at 0.5, 1, 2, 4, 6, 8, and 12 (± 2 hours) post-dose after the administration of the first dose of the first cycle. At Day 22 (Visit 5; at steady-state) blood samples will be collected prior to dosing and then, 0.5, 1, 2, 4, 6, 8, and 12 ± 2 hours post-dose. Steady state refers to patients who have received at least 5 days, or 10 consecutive doses, of investigational product. If patient is not at steady state at Day 22 (Visit 5), these assessments will be rescheduled and completed at the next visit in which steady state is achieved.

Below is the list of various PK parameters that will be calculated after Dose 1 (Day 1) and at Steady State (Day 22).

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_{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 concentration and PK parameters 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 the Covance Sample Analysis Outline document for additional details re. the PK analyses.

A listing of blood PK concentrations and parameters will be provided.

12 OTHER ANALYSES

12.1 PHARMACODYNAMICS ANALYSES

Multiple biomarkers intended to demonstrate inhibition of the molecular target, and mechanism of action will be investigated (pRSK and total pRSK) from blood and/or bone marrow aspirate samples. Additional biomarkers, including peripheral blood mononuclear cells (PBMCs) and/or DNA sequence analysis, may be identified and measured as appropriate. Descriptive statistics will be provided for pharmacodynamics data in a summary table and a listing will present all data.

12.2 ANALYSIS FOR RAS MUTATION

Analysis for RAS mutation may be performed in subjects in Part 1. For subjects enrolled in Part 2 RAS mutation information (RAS positive or negative status) will be required to confirm eligibility.

Descriptive statistics and listing of RAS mutation data will be provided.

12.3 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.

14 TABLE OF CONTENTS FOR DATA DISPLAYS

Tables, Figures, and Listings to be generated for the trial are summarized below; examples are provided in a separate attachment.

14.1 DEMOGRAPHICS SUMMARY FIGURES AND TABLES

Part II

Part II: Study Population

Table	Title	Population
Part II - Table 14.1.1.1	Summary of Analysis Populations	Enrolled Population
Part II - Table 14.1.1.2	Subject Disposition	Screened Population
Part II - Table 14.1.2	Protocol Deviations	Screened Population
Part II - Table 14.1.3.1	Demographic and Baseline Characteristics	Safety Population
Part II - Table 14.1.3.2	Demographic and Baseline Characteristics	mITT Population
Part II - Table 14.1.3.3	Demographic and Baseline Characteristics	PP Population
Part II - Table 14.1.4.1	Medical History	Safety Population
Part II - Table 14.1.4.2	Previous Cancer Surgery	Safety Population
Part II - Table 14.1.4.3	Previous Stem Cell Transplant	Safety Population
Part II - Table 14.1.4.4	Transfusion/Blood Product Use	Safety Population
Part II - Table 14.1.4.5	Prior MEK Therapies	Safety Population
Part II - Table 14.1.4.6	Previous Therapies	Safety Population
Part II - Table 14.1.5	On Study Procedures	Safety Population
Part II - Table 14.1.6.1	Prior Medications	Safety Population
Part II - Table 14.1.6.2	Concomitant Medications	Safety Population
Part II - Table 14.1.6.3	Concomitant Medications Taken for Adverse Events	Safety Population
Part II - Table 14.1.7.1	Treatment Compliance	Safety Population
Part II - Table 14.1.7.2	Exposure to Study Drug	Safety Population
Part II - Table 14.1.8	Pregnancy Test Results	Enrolled Population

14.2 EFFICACY SUMMARY FIGURES AND TABLES

Table	Title	Population
Part II - Table 14.2.1.1.1	AML Disease Response by Bone Biopsy (IWG 2003)	mITT Population
Part II - Table 14.2.1.1.2	AML Disease Response by Bone Biopsy (IWG 2003)	PP Population
Part II - Table 14.2.1.2.1	MDS Disease Response by Bone Biopsy (IWG 2006)	mITT Population
Part II - Table 14.2.1.2.2	MDS Disease Response by Bone Biopsy (IWG 2006)	PP Population

Figure	Title	Population
N/A		

14.3 SAFETY SUMMARY FIGURES AND TABLES

14.3.1 Adverse Events

Table	Title	Population
Part II - Table 14.3.1.1	Dose Limiting Toxicities	Safety Population
Part II - Table 14.3.1.2	Details of Dose Limiting Toxicities	Safety Population
Part II - Table 14.3.1.3	Summary of Dose Limiting Toxicities	Safety Population
Part II - Table 14.3.1.4	Doses Selected as MTD and RP2D	Safety Population
Part II - Table 14.3.1.4.1.1	Frequency and Reasons for Dose Delays/Interruptions	Safety Population
Part II - Table 14.3.1.4.1.2	Frequency and Reasons for Dose Reductions	Safety Population
Part II - Table 14.3.1.4.2.1	Duration of Dose Delays/Interruptions	Safety Population
Part II - Table 14.3.1.4.2.2	Duration of Dose Reductions	Safety Population
Part II - Table 14.3.1.5.1	Overview of Adverse Events	Safety Population
Part II - Table 14.3.1.5.2	Treatment Emergent Adverse Events	Safety Population
Part II - Table 14.3.1.5.3	Treatment Emergent Adverse Events Leading to Premature Discontinuation from the Study	Safety Population
Part II - Table 14.3.1.5.4.1	Treatment Emergent Adverse Events Leading to Dose Delays	Safety Population
Part II - Table 14.3.1.5.4.2	Treatment Emergent Adverse Events Leading to Dose Interruptions	Safety Population
Part II - Table 14.3.1.5.5	Treatment Emergent Adverse Events Leading to Dose Reductions	Safety Population
Part II - Table 14.3.1.5.6	Treatment Emergent Adverse Events by Relationship to BVD-523	Safety Population
Part II - Table 14.3.1.5.7.1	Treatment Emergent Adverse Events by Severity	Safety Population
Part II - Table 14.3.1.5.7.2	Treatment Emergent Adverse Events by ≥Grade 3	Safety Population

Figure	Title	Population
Part II - Figure 14.3.1.5.2	Bar Graph of Treatment Emergent Adverse Events	Safety Population

Part II - Figure 14.3.1.5.3	Bar Graph of Treatment Emergent Adverse Events Leading to Premature Discontinuation from the Study	Safety Population
Part II - Figure 14.3.1.5.5	Bar Graph of Treatment Emergent Adverse Events by Relationship to BVD-523	Safety Population
Part II - Figure 14.3.1.5.7	Bar Graph of Treatment Emergent Adverse Events by Severity	Safety Population

14.3.2 Serious Adverse Events, Deaths and Other Significant Adverse Events

Table	Title	Population
Part II - Table 14.3.2.1	Treatment Emergent Serious Adverse Events	Safety Population
Part II - Table 14.3.2.2	Treatment Emergent Serious Adverse Events Leading to Premature Discontinuation from the Study	Safety Population
Part II - Table 14.3.2.3.1	Treatment Emergent Serious Adverse Events Leading to Dose Delays	Safety Population
Part II - Table 14.3.2.3.2	Treatment Emergent Serious Adverse Events Leading to Dose Interruptions	Safety Population
Part II - Table 14.3.2.4	Treatment Emergent Serious Adverse Events Leading to Dose Reductions	Safety Population
Part II - Table 14.3.2.5	Treatment Emergent Serious Adverse Events by Relationship to BVD-523	Safety Population
Part II - Table 14.3.2.6.1	Treatment Emergent Serious Adverse Events by Severity	Safety Population
Part II - Table 14.3.2.6.2	Treatment Emergent Serious Adverse Events by ≥Grade 3 Severity	Safety Population
Part II - Table 14.3.2.7.1	Deaths	Safety Population
Part II - Table 14.3.2.7.2	Deaths by Relationship	Safety Population

Figure	Title	Population
Part II - Figure 14.3.2.1	Bar Graph of Treatment Emergent Serious Adverse Events	Safety Population
Part II - Figure 14.3.2.2	Bar Graph of Treatment Emergent Serious Adverse Events Leading to Premature Discontinuation from the Study	Safety Population
Part II - Figure 14.3.2.5	Bar Graph of Treatment Emergent Serious Adverse Events by Relationship to BVD-523	Safety Population
Part II - Figure 14.3.2.6	Bar Graph of Treatment Emergent Serious Adverse Events by Severity	Safety Population

14.3.3 Narratives

N/A

14.3.4 Laboratory Results

Table	Title	Population
Part II - Table 14.3.4.1.1	Laboratory Evaluations: Hematology	Safety Population
Part II - Table 14.3.4.1.2	Hematology Laboratory Values	Safety Population
Part II - Table 14.3.4.2.1	Laboratory Evaluations: Clinical Chemistry	Safety Population
Part II - Table 14.3.4.2.2	Clinical Chemistry Laboratory Values	Safety Population
Part II - Table 14.3.4.3.1	Laboratory Evaluations: Urinalysis	Safety Population
Part II - Table 14.3.4.4	Laboratory Evaluations: Bone Marrow Aspirate Results	Safety Population
Part II - Table 14.3.4.5	Cytogenetics	Safety Population
Part II - Table 14.3.5.1	Physical Examinations	Safety Population
Part II - Table 14.3.5.2	ECOG Performance Status	Safety Population
Part II - Table 14.3.5.3.1	Electrocardiogram	Safety Population
Part II - Table 14.3.5.3.2	Categorized Electrocardiogram	Safety Population
Part II - Table 14.3.5.4	Ophthalmological Examinations	Safety Population
Part II - Table 14.3.5.5	Vital Sign	Safety Population

Figure	Title	Population
N/A		

14.4 OTHER SUMMARY FIGURES AND TABLES

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16.2.2 Protocol Deviations

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Part II – Listing 16.2.2.2.1 Listing of Inclusion/Exclusion Criteria Deviations - Inclusion

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16.2.3 Subjects Excluded from the Efficacy Analysis

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16.2.5 Compliance and/or Drug Concentration Data

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16.2.6 Individual Efficacy Response Data

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16.2.7 Adverse Event Listings

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Part II – Listing 16.2.7.3.3 Listing of Treatment Emergent Adverse Events Leading to Study Drug Delays/Interruptions and Length of Delays/Interruptions
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Part II – Listing 16.2.7.3.5 Listing of Treatment Emergent Adverse Events Related to BVD-523
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16.2.8 Listings of Individual Laboratory Measurements

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15 REVISIONS TO SAP

The SAP dated 09DEC2015 was finalized/signed for Part 1, under protocol amendment 2. This version of the SAP has been revised to update the list of TFL shells for Part 2.

16 REFERENCES

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