STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final
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Study Drug: [^{14}C]-BVD-523

Sponsor Reference Number: 523HV001
Covance Study Number: 8353316

Clinical Phase 1

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1. STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change after an evaluation.

Covance approval:

Xin Chen, MS
Statistician

31 MAR 2017
Date

Stuart Hossack, PhD
Pharmacokineticist

31 MAR 2017
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30 March 2017
Date

2. TABLE OF CONTENTS

3. ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
AE	adverse event
A_{ef}	amount excreted in feces over sampling interval
A_{eu}	amount excreted in urine over sampling interval
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
AUC_{0-12}	area under the concentration-time curve from Hour 0 to Hour 12
AUC_{0-24}	area under the concentration-time curve from Hour 0 to Hour 24
$AUC_{0-\infty}$	area under the concentration-time curve from hour 0 extrapolated to infinity
BLOQ	below the lower level of quantification
BMI	body mass index
CBC	complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CL/F	apparent oral clearance
CLR	renal clearance
C_{max}	maximum observed plasma concentration
CSR	Clinical Study Report
C_t	the last measurable plasma concentration
CV%	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
eCRF	electronic Case Report Form
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LLOQ	lower limit of quantification
max	maximum (Max)

MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
N, n	number
NC	not calculated
NR	no result
PK	pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAP	Statistical Analysis Plan
SD	standard deviation
$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time to maximum plasma concentration
UA	urinalysis
V_z/F	apparent volume of distribution
λ_Z	the apparent terminal elimination rate constant
% F_{ef}	percent of dose excreted in feces over sampling interval
% F_{eu}	percent of dose excreted in urine over sampling interval
% AUC_{extrap}	percentage of $AUC_{0-\infty}$ determined by extrapolation

4. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final 2.0 dated 07 December 2016).

This SAP describes the planned analysis of the safety, tolerability, metabolism and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for planned analysis of the safety, metabolism, and PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between BioMed Valley Discoveries Inc. and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between BioMed Valley Discoveries Inc. and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5. STUDY OBJECTIVES

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

- The secondary objective of this study is to evaluate the safety and tolerability of a single oral dose of [^{14}C] labeled BVD-523 in healthy male subjects.

6. STUDY DESIGN

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

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

The end of the study is defined as the date the last subject completes the study. The planned duration of study conduct for each subject is up to 43 days (Screening through Discharge).

Figure 1 Study Design Schematic

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

CRU = Clinical Research Unit; PK = pharmacokinetic.

[a] Subjects will be discharged from the CRU starting on Day 8 if plasma radioactivity levels are below the limit of quantification, ≥90% of the radioactive dose is recovered, and if ≤1% of the radioactive dose is recovered in urine and feces for 2 consecutive 24-hour collection intervals. If these criteria are not satisfied by the morning of Day 8, subjects will continue to be confined in the CRU until these criteria are met, up to a maximum of Day 15.

7. TREATMENT

Subjects in this study will be administered [^{14}C]-BVD-523 as a 600-mg (approximately 200 μCi) oral dose) which will be abbreviated as [^{14}C]-BVD-523 in the TFLs.

8. SAMPLE SIZE JUSTIFICATION

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

9. DEFINITION OF ANALYSIS POPULATIONS

The **All Subjects Population** will consist of all subjects who are enrolled in the study (signed the ICF) and have study assessments recorded in the electronic Case Report Form (eCRF).

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

The **PK Population** will consist of all subjects who receive study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs within approximately 2 times median time to maximum concentration (T_{max}).

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

10. STATISTICAL METHODOLOGY

10.1 GENERAL

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum (min), maximum (max), and number of observations (n). Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.3 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

10.1.1 DEFINITION OF BASELINE AND CHANGE FROM BASELINE

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat (vital signs) and unscheduled predose readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

For safety data, mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the time point. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 REPEAT AND UNSCHEDULED READINGS

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. All results not taken at a scheduled time point for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labeled as 'Unscheduled' in the listings. Because unscheduled postdose readings are not associated with any scheduled time point, they are excluded from all summaries.

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index (BMI) will be summarized and listed. Subject disposition will be summarized and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

For each subject, the following PK parameters will be calculated, whenever possible, based on the concentrations of BVD-523, BVD-0513A, and BVD-0502A+BVD-0503A in plasma and

concentrations of total radioactivity in plasma and whole blood, using noncompartmental methods performed using Phoenix WinNonlin (Certara USA, Inc.) Version 6.4 or higher:

Parameter	**Definition**
C_{max}	maximum observed concentration
T_{max}	time to maximum concentration
AUC_{0-t}	area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to the last measurable concentration
AUC_{0-12}	area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to Hour 12
AUC_{0-24}	area under the concentration-time curve calculated using the linear trapezoidal rule from Hour 0 to Hour 24
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_Z}$ where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
% AUC_{extrap}	percentage of $AUC_{0-\infty}$ determined by extrapolation
λ_Z	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	terminal phase half-life, where $t_{1/2}$ = natural log (2)/λ_Z
CL/F	apparent oral clearance (for BVD-523 only)
V_z/F	apparent volume of distribution (for BVD-523 only)
$AUC_{0-\infty}$ Blood /Plasma Ratio	$AUC_{0-\infty}$ of total radioactivity in whole blood/$AUC_{0-\infty}$ of total radioactivity in plasma
$AUC_{0-\infty}$ Plasma BVD-523/ Total	$AUC_{0-\infty}$ of nonradiolabeled BVD-523 in plasma/$AUC_{0-\infty}$ of total

Radioactivity Ratio	radioactivity in plasma
AUC_{0-12} Blood/Plasma Total Radioactivity Ratio	AUC_{0-12} of total radioactivity in whole blood/AUC_{0-12} of total radioactivity in plasma
AUC_{0-12} Plasma BVD-523/ Total Radioactivity Ratio	AUC_{0-12} of nonradiolabeled BVD-523 in plasma/AUC_{0-12} of total radioactivity in plasma
AUC_{0-24} Blood/Plasma Total Radioactivity Ratio	AUC_{0-24} of total radioactivity in whole blood/AUC_{0-24} of total radioactivity in plasma
AUC_{0-24} Plasma BVD-523/ Total Radioactivity Ratio	AUC_{0-24} of nonradiolabeled BVD-523 in plasma/AUC_{0-24} of total radioactivity in plasma
$AUC_{0-\infty}$ Plasma Metabolites/ Total Radioactivity Ratio	$AUC_{0-\infty}$ of nonradiolabeled metabolites in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma
AUC_{0-12} Plasma Metabolites/ Total Radioactivity Ratio	AUC_{0-12} of nonradiolabeled metabolites in plasma/AUC_{0-12} of total radioactivity in plasma
AUC_{0-24} Plasma Metabolites/ Total Radioactivity Ratio	AUC_{0-24} of nonradiolabeled metabolites in plasma/AUC_{0-24} of total radioactivity in plasma

In addition, the following PK parameters will be calculated, whenever possible, for each subject based on the urine concentrations of BVD-523 and total radioactivity. Parameters for BVD-523 in urine will be calculated and reported by the Covance EC Biometrics PK group; parameters for total radioactivity (except CL_R, which will be calculated for BVD-523 only) will be calculated and reported by the Covance Radioanalysis group. Urinary parameters for total radioactivity will also be presented in the CSR tables.

Parameter	Definition
A_{eu}	amount excreted in urine over sampling interval (t1-t2) where t1 and t2 are the start and end times of the sampling interval, respectively
Cumulative A_{eu}	cumulative amount excreted in urine, calculated as the sum of the amount excreted in urine for each collection interval
CL_R	renal clearance, where $CL_R = A_{eu}/AUC_{0-\infty}$ (for BVD-523 only)
% F_{eu}	percent of dose excreted in urine over sampling interval (t1-t2), where % Excreted = 100 (A_{eu}/dose)
Cumulative % F_{eu}	cumulative percent of dose excreted in urine, calculated as the sum of the percent of dose excreted in urine for each collection interval

The following PK parameters will be calculated, whenever possible, for each subject based on the fecal concentrations of total radioactivity. Parameters for total radioactivity will be reported by the Covance Radioanalysis group in the Radioanalysis report. Fecal parameters for total radioactivity will also be presented in the CSR tables.

Parameter	Definition
A_{ef}	amount excreted in feces over sampling interval (t1-t2)
Cumulative A_{ef}	cumulative amount excreted in feces, calculated as the sum of the amount excreted in feces for each collection interval
% F_{ef}	percent of dose excreted in feces over sampling interval (t1-t2), where % Excreted = 100 (A_{eu}/dose)
Cumulative % F_{ef}	cumulative percent of dose excreted in feces, calculated as the sum of the percent of dose excreted in feces for each collection interval

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and T_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest Tmax will be reported.

The amount excreted in urine (A_{eu}) for each urine collection interval will be calculated as the product of urine concentration and urine weight; Cumulative A_{eu} 0-x hour will be calculated by summing the A_{eu} values for each collection interval over the 0-x hour period.

In addition to the PK and radioanalysis results, a discussion of the results of metabolite characterization will be included in the CSR however no tables, figures, or listings will be generated. The quantitation of parent and metabolites (concentrations and/or percent of dose), as applicable, other applicable metabolite characterization results (representative chromatograms, proposed metabolite structures, etc.), and any PK parameters calculated from the radiochromatography data will be reported in the Metabolite Profiling and Identification report. Radiochromatography PK parameters may be summarized in the CSR along with PK parameters determined from the bioanalytical data.

10.3.1.1 Criteria For Handling Concentrations below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the lower level of quantification (BLOQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLOQ value (between 2 quantifiable concentrations) and BLOQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

- If there are late positive concentration values following 2 BLOQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.

- If an entire concentration-time profile is BLOQ, the profile will be excluded from the PK analysis.

- If a predose concentration is missing, this value may be set to zero with sponsor approval.

10.3.1.2 Criteria for the Calculation of an Apparent Terminal Phase Half-Life

- **Number of Data Points**

  - At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.

- **Goodness of Fit**

  - When assessing terminal phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

  - An terminal phase half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

- **Period of Estimation**

  - Time period used for the estimation of apparent terminal phase half-lives, where possible, will be over at least 2 half-lives.

  - Where an elimination half-life is estimated over a time period of less than 2 half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value should be discussed in the study report.

- **Calculation of AUC**

  - The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}. Exceptions may be made for metabolites.

  - For any partial AUC determination (ie, AUC_{0-12} and AUC_{0-24}), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is 20% to 30% will be flagged and included in the descriptive statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported but excluded from descriptive statistics.

- **Anomalous Values**

  - If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis based on the Covance SOP. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

  - Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist and BioMed Valley Discoveries Inc.

10.3.2 Presentation of Pharmacokinetic Data

10.3.2.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLOQ or if there are missing values (eg, no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLOQ values will be set to zero.

- If an embedded BLOQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.

- Where there is NR, these will be set to missing.

- If there are less than 3 values in the data series, only the min, max, and n will be presented. The other summary statistics will be denoted as not calculated (NC). BLOQ is considered a value.

- If all the values are BLOQ, then the arithmetic mean, arithmetic SD, median, min, and max will be presented as zero.

- If the value of the arithmetic mean or median is below the LLOQ, these values will be presented as zero.

10.3.2.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

- The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max} (exception made for metabolites).

10.3.3 Pharmacokinetic Statistical Methodology

Descriptive statistics (arithmetic mean, SD, median, min, max, and number of observations) will be calculated for the PK parameters. No formal statistical analyses are planned.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse Events

A baseline sign and symptom is defined as an AE that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

Nonserious AE information observed before dosing will not be listed as an AE in the eCRF but will be listed as medical history instead, unless the AE becomes more severe postdose, in which case it will be recorded as an AE in the eCRF. Serious AEs will be recorded from the time the subject signs the ICF until study completion.

All AEs will be listed. The TEAEs will be summarized by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of at least possibly related to study treatment). Any severe or serious AEs will be tabulated. For any AEs that change

severity ratings the AE will be included only once under the maximum severity rating in the summaries.

10.4.2 Clinical Laboratory Parameters

Clinical chemistry, hematology data will be listed. In addition, all clinical chemistry panel, hematology, and UA data outside the clinical reference ranges will be listed by parameter. Any clinical chemistry, hematology, and urinalysis (UA) values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.4.3 Vital Signs

The vital signs, including systolic blood pressure, diastolic blood pressure, pulse rate, and temperature data will be summarised by time point, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by time point.

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings. Repeat and unscheduled readings will be handled as defined in Section 10.1.2.

10.4.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate. The ECG data will be listed only. Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

10.4.5 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analysed.

10.4.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

No interim statistical analyses are planned.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13. DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.