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# Title Page

## An open-label non-randomized, phase 1 single dose study to evaluate the pharmacokinetics and safety of copanlisib in subjects with impaired hepatic or renal function in comparison to healthy subjects

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|---|---|---|---|
| **Short title** | Phase 1 study of copanlisib in hepatic or renal impairment | | |
| **Bayer study drug** | Copanlisib / BAY 80-6946 | | |
| **Study purpose:** | To evaluate the effect of impaired hepatic or renal function on copanlisib | | |
| **Clinical study phase:** | I | **Date:** | 25 JUL 2018 |
| **Study No.:** | 18041 | **Version:** | 3.0 |
| **Author:** | PPD | | |



This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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# Abbreviations

| | |
|---|---|
| %AUC($t_{last}$-∞) | percentage of AUC from the last data point > LLOQ to infinity |
| AE | adverse event |
| $A_{E,ur}$ | amount excreted into urine from 0 to infinity |
| $A_{E,ur}$(x-y) | amount excreted into urine from x to y |
| ANOVA | analysis of variance |
| AUC | area under the concentration vs. time curve from zero to infinity after single (first) dose |
| AUC($t_1$-$t_2$) | AUC from time t1 to t2, e.g. AUC(4-8), AUC(0-24) |
| AUC($t_1$-$t_2$)u | AUC of unbound drug (not protein-bound) from time t1 to t2 |
| AUCu | area under the concentration vs. time curve of unbound drug (not protein-bound) from zero to infinity after single dose |
| CI | Confidence Interval |
| $C_{last}$ | last observed concentration value above lower limit of quantitation |
| CLIPS | Clinical Pharmacology Standard |
| $CL_R$ | copansilib clearance |
| CLcr | Clearance Creatinine |
| $C_{max}$ | maximum observed drug concentration in measured matrix after single dose administration |
| $C_{max,u}$ | maximum observed concentration of unbound drug (not protein-bound or free) in measured matrix after single dose administration |
| CV | coefficient of variation |
| DDI | drug-drug interaction |
| e.g. | exempli gratia (for example) |
| ECG | electrocardiogram |
| eGFR | estimated glomerular filtration rate |
| FDA | Food and Drug Administration |
| HCT | hematopoietic cell transplant |
| i.e. | id est (that is) |
| i.v. | intravenous |
| LLOQ | lower limit of quantification |
| LS-Means | least squares means |
| MDRD | Modified Diet of Renal Disease |
| MedDRA | medical dictionary for regulatory activities |
| mg | milligram |
| mL | milliliter |
| NHL | non-Hodgkin's lymphoma |
| PK | pharmacokinetic(s) |
| PKS1 | PK analysis set |
| PKS2 | PK analysis set for hepatic impairment assessment |
| PKS3 | PK analysis set for renal impairment assessment |
| PopPK | population PK |
| $R_{end}$ | last time point for λz calculation |
| $R_{start}$ | last time point for λz calculation |
| SAE | serious adverse event |
| SAF | safety analysis set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD | standard deviation |
| TEAE | treatment-emergent adverse event |

| | |
|---|---|
| $t_{½}$ | Half-life associated with the terminal slope |
| $t_{last}$ | time of last observed concentration value above lower limit of quantitation |
| $t_{max}$ | time to reach maximum drug concentration (in case of two identical $C_{max}$ values, the first $t_{max}$ will be used) |
| $V_Z$ | volume of distribution during terminal phase after intravascular |
| WHO-DD | WHO Drug Dictionary |

# 1. Introduction

Copanlisib (BAY 80-6946), approved by the Food and Drug Administration [FDA] in September 2017), is a novel, highly selective, pan-class PI3K inhibitor with potent activity against both α and β isoforms, with in vitro IC50 of 0.5 nM and 0.7 nM, respectively. This PI3K inhibitor is being developed for the treatment of advanced and refractory malignancies either as a single agent or in combination with other investigational agents. Copanlisib is the active ingredient (free base) of BAY 84-1236, the dihydrochloride salt, which for clinical use is formulated as an intravenous (i.v.) drug product solution.

Copanlisib is excreted as unchanged compound and metabolites (about 50:50) in human. Metabolism of copanlisib is mediated by cytochrome P450 CYP3A4 (> 90%) and to a minor extent by CYP1A1 (< 10%). Therefore, a low DDI potential due to several clearance pathways is anticipated.

Liver infiltration in subjects with advanced malignancies including non-Hodgkin's lymphoma (NHL) is common, and various degree of hepatic dysfunction may occur in the later stages of malignancy.

Renal failure in cancer subjects is often multifactorial including renal parenchymal invasion, tumor lysis syndrome, glomerular diseases, chemotherapy associated thrombocytic microangiopathy or hematopoietic cell transplant (HCT)-associated renal failure.

Metabolism of copanlisib is primarily mediated by the CYP3A4 isozyme. Co-administration of copanlisib at 12 mg and 60 mg with the potent inhibitor of CYP3A4 itraconazole resulted in an increased copanlisib AUC by 1.41-fold and 1.53-fold, respectively, with no effect on the $C_{max}$ at both doses. A human mass balance study (Study 16353) indicates the elimination of copanlisib is primarily via feces with 64% in feces and 22% in urine within a collection interval of 20 to 34 days. Based on the population PK (popPK) analysis, mild hepatic impairment, mild and moderate renal impairment had no significant effect on copansilib clearance (CL). The PK of copanlisib has not been studied in moderate and severe hepatic impairment and severe renal impairment.

This study will evaluate the PK and safety of a single 12-mg dose of copanlisib in subjects with moderate or severe hepatic impairment or severe renal impairment of copanlisib and in age-, gender-, and weight-matched healthy controls. The results of this study will provide guidance for drug labeling recommendations for copanlisib in these subjects.

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol BAY 80-6946 / 18041 Version 2.0, dated 28 Nov 2017 [1].

# 2. Study Objectives

The **primary** objective is to

- Investigate the PK of copanlisib following a single i.v. dose of 12 mg copanlisib in subjects with moderate hepatic (Child Pugh B), severe hepatic (Child Pugh C) or severe renal impairment compared with healthy subjects

The **secondary** objectives are to

- Evaluate the PK of M-1 metabolite
- Assess the safety and tolerability of copanlisib when administered to subjects with moderate hepatic, severe hepatic or severe renal impairment

The **exploratory** objectives are to explore the relationship between PK and hepatic and renal function parameters:

- Hepatic: Relationship between PK parameters of copanlisib AUC(0-168), AUC, $C_{max}$, AUC(0-168)u, $AUC_u$ and $C_{max,u}$ and baseline hepatic function parameters (Child-Pugh Score, total bilirubin, prothrombin time, alpha 1-acid glycoprotein and albumin)
- Renal: Relationship between PK parameters of copanlisib AUC(0-168), AUC, $C_{max}$, AUC(0-168)u, $AUC_u$ and $C_{max,u}$ and eGFR (MDRD formula) and estimated creatinine clearance (Cockcroft-Gault formula)

## 3. Study Design

This will be a multi-center, non-randomized, open-label, single-dose, parallel group, study consisting of 4 groups. The effect of moderate hepatic impairment (Child Pugh B), severe hepatic impairment (Child Pugh C) and severe renal impairment on the PK of copanlisib and M-1 will be investigated. In total, up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic investigational group will participate in the study (Table 3–1). Each subject will be administered 12 mg of copanlisib (i.v. over 1 h).

**Table 3–1: Groups**

| Group | Description | Number of evaluable subjects |
|---|---|---|
| Control group | Normal hepatic and renal function group matched to the groups of hepatic and renal impairment | 8-22 |
| Group A | Moderate hepatic impairment group:<br>Child-Pugh B (score 7-9) at the screening visit | 8 |
| Group B | Severe renal impairment group:<br>eGFR 15-29 mL/min/1.73 m2 at the screening visit based on the Modification of Diet in Renal Disease (MDRD) equation | 8 |
| Group C | Severe hepatic impairment group:<br>Child-Pugh C (score 10-15) at the screening visit | 6 |

The control group (normal hepatic and renal function) should match with the groups of hepatic and renal impairment. Matching criteria will be age, body weight, and gender. Mean age and body weight between the control group and the groups with hepatic and renal impairment should not vary by more than ±10 years and ±10 kg. Therefore, enrollment in the control group will remain open until the enrollment in the moderate and severe hepatic and severe renal impairment groups is complete and a sufficient number of matching controls have been achieved for comparison.

**Primary variables:**

- $C_{max}$, AUC and AUC(0-168) of copanlisib in plasma

**Secondary variables:**

- Number of subjects with study drug-related treatment-emergent AE (TEAE)

**Additional pharmacokinetic parameters:**

| | |
|---|---|
| Copanlisib | AUC(0-24), AUC(0-$t_{last}$), $t_{1/2}$, $t_{max}$, $t_{last}$, $V_z$, CL, $A_{E,ur}$(0-24), $CL_R$, $C_{max,u}$, AUC(0-24)$_u$, AUC(0-168)$_u$, and AUC$_u$ based on average value of unbound fraction in the 1h and 24h samples |
| BAY 84-5795 (M-1) | AUC(0-168), AUC(0-$t_{last}$), AUC, $t_{1/2}$, $C_{max}$, $t_{max}$, $t_{last}$, $A_{E,ur}$(0-24) |

**Other pharmacokinetic parameters:**

| | |
|---|---|
| Copanlisib and BAY 84-5795 (M-1) | number of points terminal, %AUC($t_{last}$-∞), $R_{start}$, $R_{end}$, $C_{last}$ |

# 4. General Statistical Considerations

## 4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Clinical Pharmacology Standard (CLIPS), Version 1.2 [2] will be used.

All data will be listed and study summary tables as well as graphical illustrations will be provided where appropriate. Whenever appropriate, summary statistics will be provided by group for the original data as well as for the change versus baseline. Frequency tables will be generated for categorical data.

This is an exploratory study; any confirmatory statistical analysis is not intended.

## 4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been treated.

Subjects who drop out may be replaced to obtain a minimum of 30 subjects (8/group except for severe hepatic impairment: 6) valid for PK of copanlisib (i.e., all blood samples for PK should be available up to 1 week [168 h]). Additional healthy subjects may be enrolled to achieve demographic matching between healthy and impaired groups in up to 22 healthy subjects valid for PK of copanlisib (i.e., up to 1 week [168 h]).

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” is regarded a “screening failure”.

### 4.3 Handling of Missing Data

Missing data will not be replaced. Analyses will be performed considering all valid data observed for the respective analysis sets.

All missing or partial data will be presented in the subject data listing as they are recorded.

### 4.4 Interim Analyses and Data Monitoring

An interim analysis will be conducted after 8 evaluable subjects with moderate hepatic impairment and 8 evaluable subjects with severe renal impairment with their corresponding matching healthy volunteers have completed the study to fulfill the first part of the postmarketing requirement as agreed with the FDA (July 2019) based on the accelerated approval of copanlisib (September 14, 2017). This interim analysis will also serve as a final analysis on the moderate hepatic impairment and severe renal impairment groups in the final clinical study report. The results of the final report will include subjects with severe hepatic impairment as agreed with FDA (July 2021).

### 4.5 Data Rules

Unless otherwise specified, the baseline assessment will be the last valid value prior to first treatment.

Repeated Measurements: If control measurements for a planned time point during screening epoch are available, the last non-missing valid value will be used for the calculation of descriptive statistics. If control measurements for a planned time point after the screening epoch are available, the first non-missing valid value (i.e. of the planned measurement) will be used for the calculation of descriptive statistics.

Data at unscheduled visit will be listed only.

## 5. Analysis Sets

### 5.1 Assignment of Analysis Sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the validity review meeting and documented in the final list of important deviations, validity findings and assignment to analysis sets.

All subjects who signed informed consent will be included in the All Enrolled Subjects evaluations. All subjects who completed the screening period and entered the treatment period will be included in the All Subjects Assigned to Treatment evaluations. In addition, the following analysis sets will be used in this study:

- All subjects who received one dose of the study medication will be included in the **safety analysis set** (**SAF**).
- All subjects with a PK profile allowing calculation of the main PK parameters will be included in the **PK analysis set** (**PKS1**).

- All hepatically impaired subjects and gender, age- and weight-matched healthy subjects with a PK profile allowing calculation of the main PK variables will be included in the **PK analysis set for hepatic impairment assessment** (**PKS2**).
- All renally impaired subjects and gender, age- and weight-matched healthy subjects with a PK profile allowing calculation of the main PK variables will be included in the **PK analysis set for renal impairment assessment** (**PKS3**).

# 6. Statistical Methodology

## 6.1 Population Characteristics

Analysis for population characteristics will be performed for the SAF-population, unless otherwise specified.

### 6.1.1 Disposition

Disposition at the end of screening will be summarized for all enrolled subjects. Disposition at the end of treatment and for follow-up will be summarized for total and each group for the SAF-population.

### 6.1.2 Demographic and Other Baseline Characteristics

Demography will be summarized using descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) or frequency tables in case of qualitative data. Analysis of demographic data will also be performed for the PKS1, PKS2 and PKS3 population if these populations differ from SAF.

### 6.1.3 Medical History

Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA, version 20.1 or higher) terms.

### 6.1.4 Prior and Concomitant Medication

The number of subjects that used prior or concomitant medication will be analyzed using frequency tables based on classified data. The classification will be done according to the WHO-DD version2017SEP.

## 6.2 Efficacy

Not applicable.

## 6.3 Pharmacokinetics/Pharmacodynamics

### 6.3.1 Pharmacokinetics

The PK analysis will be done by analyte separately, which includes analytes of copanlisib and its metabolite BAY 84-5795 (M-1). The plasma concentration-time profiles of each analyte will be summarized by group, where the groups include the age- and weight-matched healthy subject group and severe renal,a moderate hepatic and severe hepatic impaired patients. The following statistics

will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (retransformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration versus time curves of all analytes (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted by group using both linear and semilogarithmic scale.

Pharmacokinetic characteristics ($t_{max}$ and $t_{last}$ and parameters listed in the protocol as 'other parameters' excluded) will be summarized by group using the statistics mentioned above. $t_{max}$ and $t_{last}$ will be described utilizing minimum, maximum and median as well as frequency counts. Other parameters will be listed only.

Box-Whisker plots for $C_{max}$, AUC, AUC(0-168), $C_{max,u}$, AUC(0-168)$_u$, and $AUC_u$ will be presented by group.

- **Renal Impairment**

To investigate the primary objective of this study regarding renal impairment, an explorative analysis of variance (ANOVA) including group as factor will be performed on the log-transformed values of PK parameters $C_{max}$, AUC, AUC(0-168). The factor group will have two levels (matched healthy subjects and severe renal impaired subjects). Point estimates (LS-Means) as well as 90% confidence intervals (CIs) of the ratio

- severe renal impaired group/ matched healthy volunteer group

will be calculated by retransformation of the logarithmic results given by the ANOVA.

A corresponding SAS code base is outlined below:

```
PROC GLM data=dataset;
        CLASS group
        MODEL log_PK = group;
        LSMEANS group / pdiff cl alpha=0.1;
RUN;
```

Plots of the relationship between PK parameters of copanlisib and M-1 metabolite AUC(0-168), AUC, $C_{max}$, AUC(0-168)u, $AUC_u$ and $C_{max,u}$, respectively and eGFR (MDRD formula) and estimated creatinine clearance (Cockcroft-Gault formula) at screening.

Based on patient's age, weight and serum creatinine information collected at the visit, estimated creatinine clearance will be calculated as following:

for male, CLcr (mL/minute)={((l40–age (years)) x weight (kg))/(72xSerum creatinine(mg/dL))};

for female, CLcr (mL/minute)={((l40–age (years)) x weight (kg))/(72xSerum creatinine (mg/dL))}x 0.85.

The corresponding Spearman's rank correlation coefficients including the associated 95% confidence intervals will be calculated to explore any monotone relationship between the PK variables and eGFR at screening.

A linear regression analysis of PK variables versus eGFR at screening will be presented.

– **Hepatic Impairment**

To investigate the primary objective of this study regarding hepatic impairment, an explorative analysis of variance (ANOVA) including group as factor will be performed on the log-transformed values of PK parameters $C_{max}$, AUC, AUC(0-168). The factor group will have two levels (matched healthy subjects and moderate hepatic impaired subjects; or healthy subjects and severe hepatic impaired subjects). Point estimates (LS-Means) as well as 90% confidence intervals of the ratio

- Severe hepatic impaired group/ matched healthy volunteer group
- Moderate hepatic impaired group/ matched healthy volunteer group

will be calculated by retransformation of the logarithmic results given by the ANOVA.

A corresponding SAS code base is outlined above.

Plots of the relationship between PK parameters of copanlisib and M-1 metabolite AUC(0-168), AUC, $C_{max}$, AUC(0-168)u, $AUC_u$ and $C_{max,u}$, respectively and baseline hepatic function parameters (Child-Pugh Score, total bilirubin, prothrombin time, alpha 1-acid glycoprotein and albumin). The corresponding Spearman's rank correlation coefficients including the associated 95% confidence intervals will be calculated to explore any monotone relationship between the PK variables and baseline hepatic function parameters.

A linear regression analysis of PK variables versus baseline hepatic function parameters will be presented.

A confirmatory statistical analysis is not intended in this study.

### 6.3.2 Pharmacodynamics

Not applicable.

## 6.4 Safety

### 6.4.1 Adverse Avents

Individual listings of adverse events (AEs) will be provided. The incidence of TEAEs and drug-related TEAEs as well as TEAEs with treatment number and worst severity, respectively, will be summarized by group using MedDRA terms (version 20.1 or higher). Listings of deaths, SAEs and AEs leading to discontinuation (death and serious AEs excluded) will be provided.

Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study medication up to 30 days after end of treatment with study medication.

### 6.4.2 Other Safety Parameters

Quantitative data for safety (e.g. hematology, coagulation, clinical chemistry, urinalysis, vital signs, ECG) will be described by descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) and will be presented by each group for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

Laboratory data outside the reference range will be listed and flagged with 'L' for low and 'H' for high. Additional tables with all abnormal values will be presented.

Graphical displays of individual data as well as mean values with standard deviation will be included.

## 7. Determination of Sample Size

The study population will consist of up to 44 evaluable male and female subjects with 8-22 evaluable subjects in the control group, 8 evaluable subjects each in the moderate hepatic and severe renal impairment investigational group, and 6 evaluable subjects in the severe hepatic impairment investigational group. The sample size of 8 subjects in each of the groups with impaired moderate hepatic and severe renal function and 6 subjects in the severe hepatic impairement group has been selected based on practical consideration and following the FDA guidance [3] [4]. In copanlisib studies 12871 and 16270, the standard deviation (SD) for log-transformed AUC(0-168) or AUC was estimated between 0.33 and 0.40. For the current study, we assume the SD of 0.40 for log-transformed AUC(0-168). The PK parameter AUC(0-168) is considered appropriate for sample size estimation as in Study 16270 the extrapolation for calculation of AUC was only 4.8% of AUC(0-168). Further, based on the PK data from study 12871, the inter-subject variability for copanlisib PK exposure was estimated to be 46.5% for AUC(0-168) and 73.3% for $C_{max}$ in terms of geometric coefficient of variation. In study 16270, the inter-subject variability for $C_{max}$ was 63.2% in terms of geometric mean CV. The AUC(0-168) value has been considered for sample size estimation as a suitable PK parameter because of the higher uncertainty around of the $C_{max}$ especially for an i.v. drug. For AUC(0-168), a sample size of 8 eligible subjects each in the control, moderate hepatic and severe renal impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within a 2-fold difference, that is, within limits of 50% to 200% for AUC(0-168). This can be shown in Table 7–1 based on different observed ratios.

**Table 7–1: 90% Confidence interval for copanlisib with N=8 per group**

| Observed Ratio | 90% CI for the ratio |
|---|---|
| 1 | (0.685, 1.461) |
| 1.1 | (0.753, 1.607) |
| 1.2 | (0.822, 1.753) |
| 1.3 | (0.890, 1.899) |

A sample size of 6 eligible subjects per each in the control and severe hepatic impairment investigational group would provide an approximately 90% chance for the 90% confidence interval for the ratio of geometric least-squares means between impaired subjects and healthy subjects to be within an approximately 2-fold difference, that is, within limits of 50% to 207% for AUC(0-168) as shown in Table 7–2 based on different observed ratios.

**Table 7–2: 90% Confidence interval for copanlisib with N=6 per group**

| Observed Ratio | 90% CI for the ratio |
|---|---|
| 1 | (0.628, 1.593) |
| 1.1 | (0.691, 1.752) |
| 1.2 | (0.753, 1.911) |
| 1.3 | (0.816, 2.07) |

# 8. Document history and changes in the planned statistical analysis

- Approval of SAP v1.0 (25 Jul 2017)
- Final SAP v2.0 updated on 07 MAY 2018 according to the protocol amendment 1 forming integrated protocol Version 2.0, dated 28 Nov 2017
- Final SAP v3.0 updated on 25 JUL 2018 by adding the clearance creatinine calculation

# 9. References

[1] d. 1. M. 2. Clinical Study Protocol BAY 80-6946 / 18041 Version 1.0.

[2] V. 1. d. 1. D. 2. Clinical Pharmacology Standards (CLIPS).

[3] d. a. a. i. o. d. a. l. M. 2. Guidance for Industry: Pharmacokinetics in patients with impaired hepatic function: study design.

[4] d. a. a. i. o. d. a. l. M. 2. Guidance for Industry: Pharmacokinetics in patients with impaired renal function: study design.