Statistical Analysis Plan

CicloMed LLC

CPX-POM-002

A Window of Opportunity Study to Characterize the Safety, Dose Tolerance, Pharmacokinetics and Pharmacodynamics of CPX-POM in Patients with Newly Diagnosed or Recurrent Bladder Tumors

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Approval

Upon review of this document the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
ChIP	Chromatin Immunoprecipitation
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICH	International Conference on Harmonization
IQR	Interquartile Range
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
NCI	National Cancer Institute
NCS	Not Clinically Significant
PS	Pharmacokinetic Set
PT	Preferred Term
RNA	Ribonucleic Acid
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor-infiltrating Lymphocytes
TLFs	Tables, Listings, and Figures
TURBT	Transurethral Resection of Bladder Tumor
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of CicloMed LLC Protocol CPX-POM-002 [A Window of Opportunity Study to Characterize the Safety, Dose Tolerance, Pharmacokinetics, and Pharmacodynamics of CPX-POM in Patients with Newly Diagnosed or Recurrent Bladder Tumors]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

The primary purpose of this study is to evaluate safety and dose tolerance as well as investigate the mechanisms of action of CPX-POM in patients with newly diagnosed or recurrent, untreated or intravesical treatment completed >6 months before the current diagnosis, resectable bladder tumors, after administration of the recommended phase 2 dose (RP2D) to the target patient population. The patient population selected will have pre-dose tumor samples obtained by in-office cystoscopy available and will be scheduled for transurethral resection of a bladder tumor (TURBT), and therefore will not need to undergo additional, study-specific, invasive procedures.

2.1 Primary Objective

The primary objective of the study is to characterize the safety and dose tolerance of CPX-POM administered as 900 mg/m^2 IV by 20-minute IV infusion once daily for 5 days to patients with newly diagnosed or recurrent bladder tumors who will be scheduled to undergo TURBT.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the number of patients with treatment-related AEs
- To elucidate mechanisms of CPX-POM action on bladder tumor tissues emplying an unbiased approach, using ribonucleic acid sequencing (whole transcriptome shotgun sequencing, RNA-seq) and chromatin immunoprecipitation-DNA sequencing (ChIP-seq)
- To determine the change in bladder tumor tissue cell proliferation, Notch and Wnt cell signaling pathways, as well as bladder tumor tissue CD8+ tumor-infiltrating lymphocytes (TIL) via immunohistochemistry
- To determine bladder tumor tissue-to-plasma and tissue-to-urine CPX concentration ratios

2.2 Exploratory Objective

The exploratory objective of the study is to determine urine β-glucuronidase activity.

3. STUDY DESIGN AND PLAN

This will be an open-label study to determine the safety, dose tolerance, pharmacokinetics, and pharmacodynamics of CPX-POM in patients with newly diagnosed or recurrent, untreated or intravesical treatment completed >6 months before the current diagnosis, resectable tumors. Approximately 12 patients will be enrolled and treated with 900 mg/m^2 CPX-POM administered IV over 20 minutes once per day for 5 days followed by TURBT on Day 5 after the fifth dose. TURBT will be performed 2 to 6 hours following drug administration on Day 5.

Pretreatment bladder tumor tissues will be obtained at the time of in-office cystoscopy by cold cup biopsy within 4 weeks of TURBT. Posttreatment bladder tumor tissues will be obtained at TURBT. Bladder tumor tissues will undergo pathological evaluation at each site.

Prior to administration of the first CPX-POM dose on Day 1, pre-dose blood (plasma) and urine (clean catch) samples will be collected. At the time of TURBT on Day 5, one 3-mL blood (plasma) sample and a urine specimen will be collected for measurement of CPX-POM concentrations. The full schedule of assessments can be found in Table 1 of the protocol.

Patients will be followed for at least 30 days after the last dose of CPX-POM for safety.

4. DETERMINATION OF SAMPLE SIZE

There were no formal sample size calculations conducted for this study as there are no formal statistical analyses planned. The estimated number of patients for this study is 12.

5. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Conference on Harmonisation (ICH) numbering convention will be used for all TLFs. Continuous variables will be summarized with sample size (n), mean, standard deviation (SD), median, interquartile range (IQR), minimums, and maximums. Other summaries (e.g., quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate. Mean, median, and IQRvalues will be formatted to one more decimal place than the measured value. SD will be formatted to two more decimal places than the measured value. Minimum and Maximum values will be presented to the same number of decimal places as the measured value. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher. Tables, listings, and figures will be provided in PDF format.

5.1 Missing or incomplete dates

The most conservative approach will be systematically considered. If the AE onset date is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e.,

considered a TEAE) except if the partial onset date or other data such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered as both a prior and concomitant treatment.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as '01'.
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2021 is estimated as 01-JAN-2021).
- If the start date is completely missing and the stop date is either after the dose of study drug or completely missing, the start date will be estimated to be the day of study drug dosing. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing while January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day will be assumed to the last of the month (e.g., ??-JAN-2021 will be treated as 31-JAN-2021).
- If both the day and month of resolution are unknown, the event will be assumed to have ceased on the last known date on the study or the last day of the year (e.g., ??-???-2021 will be treated as 31-DEC-2021), whichever occurs earlier.
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug and will be imputed using the last known date on the study.

6. ANALYSIS SETS

The following analysis sets will be used:

- Safety Set (SS) will consist of all patients who receive at least 1 dose of study drug. All safety and pharmacodynamic (PD) data will be analyzed using the safety set.

- Pharmacokinetic Set (PS) will consist of all patients for whom a tissue, plasma, and/or urine sample is obtained and analyzed for determintation of plasma drug and metabolites concentration.

7. STUDY POPULATION

7.1 Patient Disposition

Patient disposition information will be summarized for all patients by treatment group (only 900 mg/m^2 CPX-POM). Summaries will include: the number of patients screened, the number of patients in each analysis set, the number of patients completing the study, the number of patients completing 5 days of dosing with CPX-POM and who undergo TURBT from which tissue, blood, and urine samples were collected, the number of patients who completed the Day 35 Follow-up Visit, the number of patients who died and the primary cause of death, the number of patients who had an autopsy, and the primary reason for discontinuation.

7.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock.

Major protocol deviations will be summarized by deviation category and listed.

7.3 Demographics and Baseline Characteristics

Demographics including age, sex at birth, ethnicity, race and childbearing potential will be listed and summarized. Descriptive statistics will be presented for age. Frequency counts and percentages will be presented for sex, ethnicity, race, ECOG status and childbearing potential.

Baseline characteristics of height (measured at screening), weight (measured at Visit 1), BSA, and whether bladder tumor is newly diagnosed or recurrent will be summarized with descriptive statistics. BSA will be calculated by the site personnel using the Dubois method using screening height and baseline weight measurements.

Medical history will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.1). Overall summaries will be provided by system organ class and preferred terms ordered by descending incidence of system organ class and preferred term within each system organ class. Medical history will also be listed.

7.4 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms will be mapped to Anatomical Therapeutic Chemical (ATC) class and Preferred Names using the World Health Organization (WHO) Drug Dictionary Enhanced (version B3/September 2020).

Concomitant medications are defined as medications that started on or after the treatment start date or were ongoing at the date of treatment start. Prior medications are defined as medications that started and stopped prior to the date of treatment start. Medications taken within 30 days

before baseline (Study Visit 2) must be recorded as a prior medication. Prior and concomitant medications will be listed.

8. EFFECTIVENESS ANALYSES

The primary objective of this study is to characterize the safety and dose tolerance of CPX-POM, there are no planned efficacy analyses. Pharmacokinetic and pharmacodynamic analyses of bladder tumor tissue, plasma and urine samples will be reported separately.

9. SAFETY ANALYSES

All safety analyses will be based on the SS population. Data will be presented using descriptive statistics and no formal hypothesis testing will be implemented.

9.1 Baseline Values

Baseline is be defined as the measurement taken at baseline safety assessment Visit #2 (Study Day 1). If that measurement is not available, baseline is defined as the last non-missing measurement recorded prior to CPX-POM administration.

9.2 Handling of Dropouts or Missing Data

No imputations will be made for missing values. Summaries will be based on observed data only.

9.3 Extent of Exposure

CPX-POM exposure will be summarized by visit and overall. Descriptive statistics for study drug administration will be presented for total dose administered and volume infused. Frequency counts and percentages will be presented for number of patients administered CPX-POM, number of infusions interrupted and the reason for interruption. CPX-POM adiminstration data will also be listed.

9.4 Adverse Events

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after first CPX-POM dosing and those existing AEs that worsened during the study. This will not include AEs that are due to the operative TURBT procedure. If it cannot be determined whether the AE is treatment emergent due to incomplete or missing data, then it will be considered treatment emergent. Verbatim terms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.1).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. The following summaries will be provided:

- Overall summary of AEs
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and highest intensity
- Related TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Serious Related TEAEs by system organ class and preferred term
- TEAEs leading to study discontinuation by system organ class and preferred term
- TEAEs resulting in death

Related events will be any event having the causality field marked as "Related" or missing on the Adverse Event eCRF page. Intensity (Grade) of AEs will be based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) (5.0).

All AEs will be provided in a listing.

9.5 Clinical Laboratory Evaluation

Laboratory parameters (clinical chemistry, hematology, urinalysis) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized.

Graded laboratory abnormalities will be defined using the grading scheme based on NCI CTCAE (5.0). The incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug, will be summarized by Grade. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

All laboratory parameters and pregnancy test results will be provided in listings.

9.6 Vital Signs

Vital signs (blood pressure, respiratory rate, heart rate, oxygen saturation and temperature) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized.

All vital signs data will be provided in listings.

9.7 Physical Examination

Physical examination results, including weight, will be listed. This listing will include data from each full physical exam (Screening and Follow-up/End of Treatment visits) and also assessments for physical symptoms/toxicities (recorded at each visit during the treatment period).

9.8 Electrocardiogram

Overall interpretation results for ECG will be summarized using shift tables (Normal, Abnormal NCS, Abnormal CS) comparing baseline to follow-up. Descriptive statistics at baseline and at each post-baseline time point as well as changes from baseline will be summarized for each ECG parameter.

All ECG results will be listed.

9.9 Other Safety Measurements

The following safety measurements collected will also be provided in listings:

- Echocardiogram
- Chest X-Ray or CT Scan
- Pregnancy Test Results

9.10 Study Procedures

The details of the following procedures will be provided in listings:

- Cytoscopy/Biopsy Procedures
- Transurethral Resection of Bladder Tumor (TURBT)

10. PHARMACOKINETIC ANALYSES

Tissue, plasma, and urine concentrations of CPX-POM and its metabolites will be determined by GLP-validated liquid chromatography with tandem mass spectrometry LC-MS/MS assays and results will be presented in by-patient listings.

Bladder tumor tissue-to-plasma and tissue-to-urine CPX concentration ratios will be calculated for each patient and listed.

Urine β–glucuronidase activity, expressed as units of activity per milliliter of urine as well as units of activity per milligram of urine creatinine, will be measured for each patient and listed.

These results will be reported separately.

11. PHARMACODYNAMIC ANALYSES

Bladder tumor tissues will be analyzed using single cell sequencing to elucidate mechanisms of CPX-POM action. To determine the change in bladder tumor tissue cell proliferation, Notch and Wnt cell signaling pathways, as well as bladder tumor tissue CD8+ TIL, immunohistochemistry will be performed on paraffin-embedded slides.

These results will be reported separately.

12. REFERENCES

13. SOFTWARE

SAS Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

14. SAP REVISIONS

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision