CicloMed LLC

CLINICAL STUDY PROTOCOL

Study Title:	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
Sponsor:	[redacted]
IND No.:	132545
Indication:	Non-Muscle Invasive Bladder Cancer
Protocol ID:	CPX-POM-002
Protocol Versions/Dates:	Original Protocol Version 1.0 /13 July 2020

SPONSOR SIGNATURE PAGE

[redacted]

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

Version 1.0, 13 July 2020

This protocol has been approved by CicloMed LLC. The following signatures document this approval.

[redacted]

[redacted] (Date)

[redacted]

[redacted] (Date)

INVESTIGATOR PROTOCOL AGREEMENT

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

Version 1.0, 13 July 2020.

By my signature, I

- Confirm that my staff and I have carefully read and understand this protocol and the Investigator's Brochure (IB) and are thoroughly familiar with the appropriate use of the investigational drug described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study procedures provided by the Sponsor, CicloMed LLC.
- Agree to comply with United States (US) Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement changes to the protocol without agreement from the Sponsor and prior written approval (where required) from the Institutional Review Board (IRB), except when necessary to eliminate an immediate hazard to the subjects.
- Agree to onsite monitoring of the case report forms (CRFs) and source documents by the Sponsor or designee and to audit by the Sponsor or designee and appropriate regulatory authorities, including, but not limited to, the FDA and IRB inspectors.
- Agree to supervise the conduct of the study and maintain responsibility for training and supervising all personnel who have been delegated responsibilities under my leadership. The protocol and other important study materials will be available to study staff throughout the conduct of the study.

_____ _____

Investigator's Signature Date

_____

Print Name

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1.1. Synopsis

Study Title:	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
IND Number:	132545
Study Centers Planned:	One center in the United States
Objectives:	The primary objective is: • To characterize the safety and dose tolerance of CPX-POM administered as 900 mg/m^2 by 20-minute intravenous (IV) infusion once daily for 5 days to patients with newly diagnosed or recurrent bladder tumors who will be scheduled to undergo transurethral resection of a bladder tumor (TURBT) The secondary objectives are: • To determine the number of patients with treatment-related adverse events (AEs) • To elucidate mechanisms of CPX-POM action on bladder tumor tissues employing 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 ciclopirox (CPX) concentration ratios

Study Design:	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. Patients will be followed for at least 30 days after the last dose of CPX-POM for safety.
Number of Patients Planned:	Approximately 12 patients will be enrolled.
Target Population:	The target population for this study is patients with newly diagnosed bladder tumors, inclusive of recurrent disease, who are treatment-naïve or had treatment completed >6 months before screening, and will be scheduled to undergo TURBT
Duration of Study:	Patients will be in this study for approximately 9 weeks: up to a 28-day screening period, a 5-day treatment period, and a 30-day follow-up period.
Diagnosis and Main Eligibility Criteria:	Patients eligible for enrollment will be adults who are likely to have a new bladder tumor based on clinical presentation or who are at high risk for tumor recurrence based on previous history, which is subsequently confirmed cystoscopically and will be scheduled to undergo TURBT. Patients must be treatment-naïve or had treatment completed >6 months before screening, and have an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2.
Test Product, Dose, and Mode of Administration:	Patients will begin treatment with CPX-POM on a Monday, 4 days before the date of scheduled TURBT on a Friday. Patients will receive CPX-POM 900 mg/m^2 by 20-minute IV infusion once daily for 5 days followed by TURBT after the last dose on Day 5.
Reference Therapy, Dose, and Mode of Administration:	Not applicable.
Criteria for Evaluation:	<u>Safety and Dose Tolerance:</u> Safety and tolerability will be based on an assessment of AEs, physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory tests, ophthalmologic assessments, and concomitant medications.

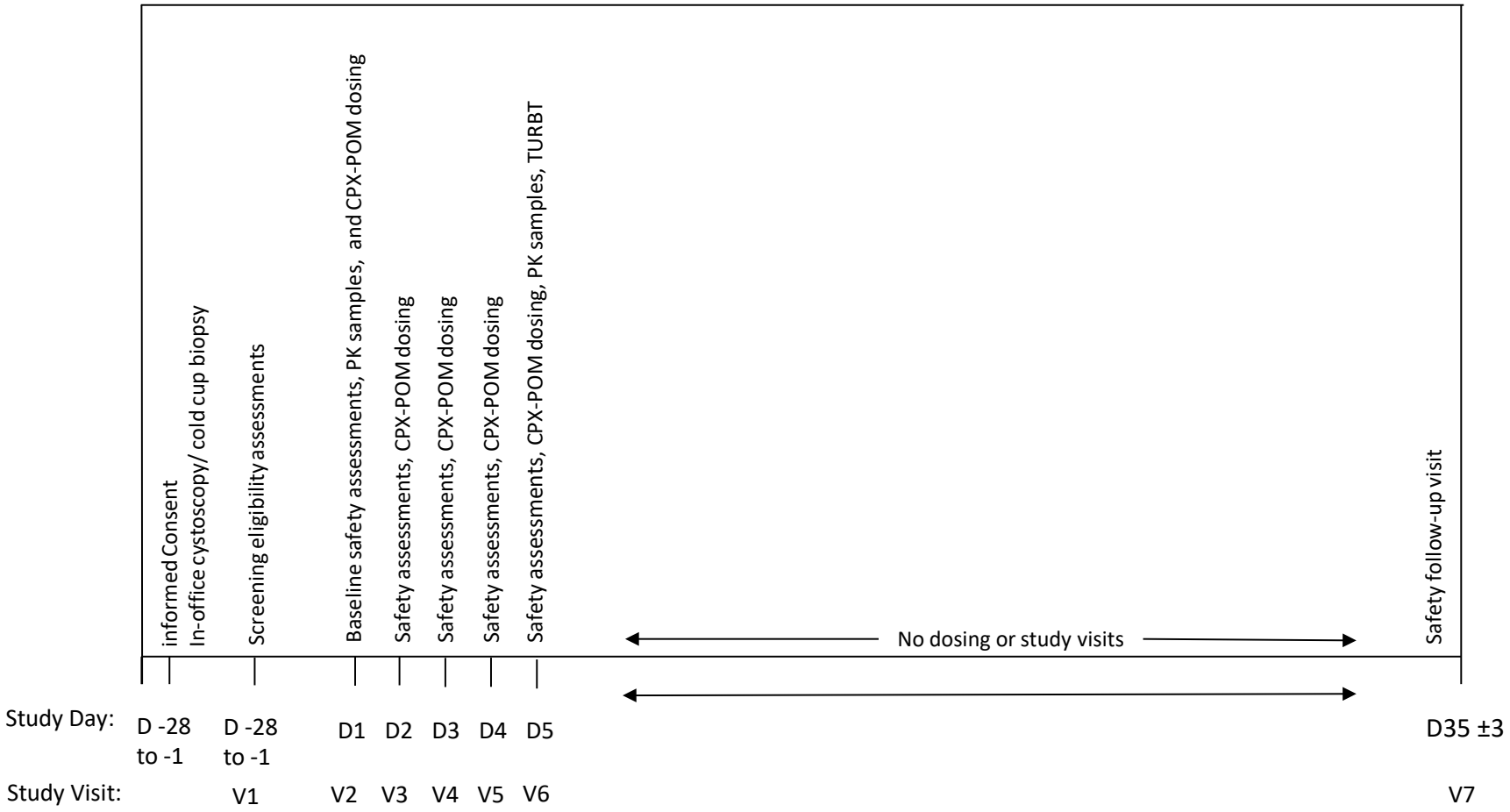
	Pharmacokinetics and Pharmacodynamics Bladder cancer tissue will be obtained at the time of in-office biopsy during cystoscopy and at TURBT and will be evaluated by the departments of pathology at the clinical sites. Bladder tumor tissues will be analyzed using RNA-seq and ChIP-seq to elucidate mechanisms 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+ TILs, immunohistochemistry will be performed on paraffin-embedded slides. Concentrations of CPX-POM, CPX, and ciclopirox glucuronide (CPX-G) in urine, plasma, and tumor tissue collected at the time of TURBT on Days 1 and 5 will be determined by Good Laboratory Practices (GLP)-validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Urine β-glucuronidase activity will be determined in the urine specimens collected on Days 1 and 5 by enzyme linked immunosorbent assay (ELISA).
Statistical Methods:	Safety and Dose Tolerance: Safety data will be presented in by-patient listings. Categorical safety endpoints will be summarized by frequency of events/abnormalities for each dose group and overall. Continuous safety endpoints will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation, median, first quartile [Q1], third quartile [Q3], minimum, maximum) for each dose group and overall. Pharmacokinetics and Pharmacodynamics: By-patient listings of the results of bladder tumor tissues RNA-seq and ChIP-seq analyses will be provided. By-patient listings of immunohistochemical analysis of pre-treatment and TURBT bladder tumor tissues will be provided. By-patient listings of concentrations of CPX in tumor, plasma, and urine will be provided. Bladder tumor tissue-to-plasma and tissue-to-urine CPX concentration ratios will be presented for each patient. By-patient listings of urine β-glucuronidase activity will be provided.

This study will be conducted in accordance with the guidelines of current GCPs including archiving of essential documents.

1.2. Study Diagram

The study design is illustrated in Figure 1.

Figure 1. Study Design



Abbreviations: D = day, PK = pharmacokinetics; TURBT = transurethral resection of bladder tumor; V = visit.

1.3. Schedule of Assessments

The schedule of assessments is shown in Table 1.

Table 1. Schedule of Assessments

Study Procedure	Screening Period	Treatment Period					Follow-up Period / ET [1]
Study Days:	D -28 to D -1	D1	D2	D3	D4	D5	D35
Study Visits:	V1	V2	V3	V4	V5	V6	V7
Informed consent	X						
Cystoscopy / cold cup biopsy	X						
Inclusion/exclusion criteria	X	X					
ECOG Performance Status	X						
Medical history	X						
Pregnancy test [2]	X	X					X
MUGA or ECHO	X						
Chest X-ray or CT scan	X						
Obtain tumor tissue sample [3]	X					X	
Hematology [4]	X	X		X		X	X
Clinical chemistry [5]	X	X		X		X	X
Urinalysis [6]	X	X		X			X
Full physical exam [7]	X						X
Assess for physical symptoms/toxicities [7]		X	X	X	X	X	
Vital signs [8]	X	X	X	X	X	X	X
ECG [9]	X	X				X	X
Adverse events [10]	X	X	X	X	X	X	X
Concomitant medications [11]	X	X	X	X	X	X	X
PK blood sample [12]		X				X	
PK urine sample [13]		X				X	
Body surface area [14]		X					
CPX-POM infusions [15]		X	X	X	X	X	
TURBT [16]						X	

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BSA = body surface area; BUN = blood urea nitrogen; CPX-G = ciclopirox glucuronide; CPX-POM = ciclopirox phosphoryloxymethyl ester; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EDTA = ethylenediamine tetraacetic acid; eGFR = estimated glomerular filtration rate; ELISA = enzyme linked immunosorbent assay; ET = early termination; GGT = gamma glutamyl transferase; IV = intravenous; LC-MS/MS = liquid chromatography-tandem mass spectrometry; MUGA = multi-gated acquisition; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; QTc = corrected QT interval; RBC = red blood cell; RC = radical cystectomy; SAE = serious adverse event; TURBT = transurethral resection of a bladder tumor; V = visit; WBC = white blood cell.

1. Safety follow-up assessments will be performed within 30 days (±3 days) after the last dose of CPX-POM. Or, in the event that a patient discontinues from the study prematurely, the site will make every effort to perform the assessments listed for this study visit.
2. Pregnancy tests will be required only for women of childbearing potential at Screening and before dosing on Day 1. Urine or serum pregnancy tests are acceptable.
3. Pre-treatment bladder tumor tissue sample will be obtained during in-office cystoscopy by cold cup biopsy within 4 weeks of TURBT. Post-treatment bladder tissue sample will be obtained at surgical resection (TURBT) on Day 5.
4. Hematology will include measurement of hemoglobin, hematocrit, platelets, RBC, reticulocytes, and WBC with differential.
5. Clinical chemistry will include measurement of potassium, sodium, chloride, glucose, BUN, creatinine, creatinine clearance, ALT, AST, GGT, alkaline phosphatase; indirect bilirubin, direct bilirubin, total bilirubin, total protein, albumin, calcium, bicarbonate, magnesium, phosphate, lipase, and amylase.
6. Urinalysis will include color, turbidity, pH, specific gravity, glucose, ketones, nitrites, bilirubin, urobilirubin, protein, RBCs, WBCs, epithelial cells, casts, crystals, and bacteria, and eGFR at Screening only.
7. A full physical examination will be conducted at Screening and at Visit 7/Follow-up. At each other study visit, patients will be assessed for continued dosing and any possible physical symptoms/toxicities and a physical examination may be performed, if indicated. Body weight should be measured at each study visit. Height should be measured at Screening.
8. Vital signs will be measured before any blood draws scheduled for the same time point. Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, and temperature.
9. At Screening, 12-lead ECGs will be performed in triplicate, with each measurement separated by 2 minutes. The average of the 3 screening ECGs will be used to calculate QTc interval to determine study eligibility. Thereafter, single 12-lead ECGs will be performed for all patients prior to drug administration on Days 1 and 5 and at the Final Study visit.
10. All AEs and SAEs will be collected from the signing of the informed consent form through the time of TURBT. Starting at TURBT, only AEs related to CPX-POM treatment should be recorded; AEs related to the TURBT will not need to be recorded.
11. All concomitant medications will be recorded from the time of Screening up to the time of TURBT. Starting at TURBT, only medications associated with an AE related to CPX-POM treatment need to be recorded; routine medications and medications associated with the TURBT procedure do not need to be recorded.
12. Single blood (plasma) samples will be taken on Day 1 prior to CPX-POM administration and on Day 5 at the time of TURBT. Concentrations of CPX-POM, CPX, and CPX-G will be determined in these samples by LC-MS/MS. The date and time of sample collection will be recorded.

13. A clean catch urine sample will be collected on Day 1 prior to CPX-POM administration. A second urine specimen will be collected on Day 5 at the time of TURBT. Concentrations CPX-POM, CPX, and CPX-G will be determined in these samples by LC-MS/MS. Urine β-glucuronidase activity will also be determined in these samples by ELISA.
14. BSA will be calculated by the site personnel using the Dubois method of calculation using screening (Visit 1) height and baseline (Visits 2) weight measurements.
15. CPX-POM infusions will be administered as 900 mg/m^2 20-minute IV infusion once daily for 5 days. Patients will be observed for at least 1 hour after completion of each infusion of CPX-POM.
16. TURBT will be performed within 2 to 6 hours after the last dose of CPX-POM has been administered on Day 5.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
BSA	body surface area
ChIP-seq	chromatin immunoprecipitation-DNA sequencing
CNS	central nervous system
CPX	ciclopirox
CPX-G	ciclopirox glucuronide
CPX-O	ciclopirox olamine
CPX-POM	ciclopirox phosphoryloxymethyl ester (ciclopirox prodrug)
CRF	case report form(s)
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IRB	institutional review board
IV	intravenous
MIBC	muscle invasive bladder cancer
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
n	number of subjects
NCI	National Cancer Institute
NMIBC	nonmuscle invasive bladder cancer
NOAEL	no observed adverse effect level

NYHA	New York Heart Association
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RC	radical cystectomy
RNA	ribonucleic acid
RNA-seq	RNA-sequencing or whole transcriptome shotgun sequencing (use of next-generation sequencing to reveal the presence and quantity of RNA in a biological sample)
RP2D	recommended phase 2 dose
SAE	serious adverse event
SOC	system organ class
TIL	tumor infiltrating lymphocyte
TURBT	transurethral resection of a bladder tumor
ULN	upper limit of the normal range

2. INTRODUCTION

2.1. Background on CPX-POM

Fosciclopirox (CPX-POM) is a prodrug of ciclopirox (CPX). CPX is a synthetic antifungal agent approved for topical dermatologic use in the treatment of a broad spectrum of fungal organisms (Gupta, 2001). CPX and ciclopirox olamine (CPX-O) are contained in a number of marketed topical drug products. CPX also exerts antibacterial activity against many Gram-positive and Gram-negative bacteria (Abrams et al, 1991). CPX is a hydroxypyridone that is structurally unrelated to other antifungal agents and has a unique and complex mode of action. CPX is thought to act through the chelation of polyvalent metal cations, such as iron and aluminum, resulting in the inhibition of the metal-dependent enzyme systems (e.g., cytochromes, catalase, peroxidase), thus disrupting cellular activities, such as inhibiting degradation of peroxides within the fungal cells (Gupta and Plott, 2004) and mitochondrial electron transport processes and energy production (Sakurai et al, 1978; Gupta et al, 1994). It is also thought that CPX affects the cytoplasmic membranes, inhibiting transport of essential elements in the fungal cell, disrupting the synthesis of DNA, ribonucleic acid (RNA), and protein (Gupta and Plott, 2004). In addition, CPX may have anti-inflammatory activity as demonstrated by its ability to inhibit the synthesis of prostaglandins and leukotrienes in human polymorphonuclear cells (Abrams et al, 1991) and to inhibit the formation of 5-lipoxygenase and ciclo-oxygenase (Bohn and Kraemer, 2000; Hanel et al, 1991).

CPX has demonstrated in vivo and/or in vitro anticancer activity in at least 17 types of solid tumor and hematologic cancers (CPX-POM Investigators Brochure, 2017). CPX modulates iron-dependent enzymes and signaling pathways resulting in inhibition of cell growth, proliferation, and survival. CPX has been demonstrated to chelate intracellular iron in human cancer cells (Kwong et al, 2015; Eberhard et al, 2009; Sidarovich et al, 2015), which plays an important role in cancer cell death resulting from exposure to CPX (Clement et al, 2002; Szüts and Krude, 2004; Eberhard et al, 2009; Sidarovich et al, 2015). CPX exposure altered expression of 54 proteins in stem cells, including those associated with nucleotide binding, biosynthetic processes, gene expression, regulation of transcription, cell cycle processes, RNA and messenger RNA (mRNA) processing, and embryonic development (Dihazi et al, 2011).

CicloMed is aware of 2 published reports of CPX-O administered orally to humans (Minden et al, 2014; Kellner et al, 1981). Following oral administration of CPX-O to patients with refractory hematologic malignancies, evidence of pharmacodynamic (PD) activity was observed (Minden et al, 2014; Song et al, 2011). Administration by the oral route of administration, however, is not feasible because of dose-limiting gastrointestinal toxicity and poor oral bioavailability due to high first pass effect (Minden et al, 2014).

Scientists at the University of Kansas synthesized the phosphoryloxymethyl ester of CPX, CPX-POM to enable parenteral administration of CPX. In contrast to CPX and CPX-O, CPX-POM has high water solubility and is readily formulated for parenteral administration.

Pharmacokinetic (PK) studies in laboratory animals showed that CPX-POM is rapidly and completely metabolized to its active metabolite, CPX, which then disappears from plasma following systemic administration of CPX-POM. Following systemic administration of CPX-POM, the dose is eliminated from the body via renal clearance of CPX and the inactive glucuronide metabolite of CPX (CPX-G).

In rats, intravenous (IV) CPX-POM administered for 28 consecutive days did not cause mortality or changes in body weight, food consumption, ophthalmology, hematology, coagulation, clinical chemistry, urinalysis, or organ weights. There were no test item-related findings grossly or microscopically at the highest dose level tested (50 mg/kg/day). Test item-related transient clinical signs, including slight to moderate decreased activity, increased respiration, eating-like behavior, and slight to moderate incoordination were noted immediately after dosing at 50 mg/kg/day. The no observed adverse effect level (NOAEL) in rats was 25 mg/kg/day in males and 50 mg/kg/day in females.

In dogs, CPX-POM administered for 28 consecutive days did not cause mortality or changes in body weight, food consumption, electrocardiogram (ECG) parameters, hematology, coagulation, clinical chemistry, urinalysis, or organ weights. There were no test item-related findings grossly or microscopically at dose levels up to 30 mg/kg/day. Test item-related transient clinical signs such as salivation, fecal changes, aggression, shaking, and tremors were noted after dosing at the highest dose level tested on the study (30 mg/kg/day). Convulsion was apparent in one dog on a single occasion. Test-item related ophthalmic changes were noted in 3/10 dogs treated with 30 mg/kg/day. Thus, the NOAEL in dogs was determined to be 10 mg/kg/day and the highest non-serious toxic dose (HNSTD) in the dog was determined to be 30 mg/kg.

The first study of CPX-POM in patients (Study CPX-POM-001) has been initiated. A total of 19 patients with a histologically- or cytologically-confirmed solid tumor refractory to standard therapy were enrolled in the Dose Escalation cohorts, 6 males and 13 females ranging in age from 20 to 86 years. The starting dose of CPX-POM was 30 mg/m^2 administered once per day on Days 1 to 5 of each 21-day cycle. Doses were escalated per protocol up to 1200 mg/m^2. The number of cycles of CPX-POM administered ranged from 1 to 6 per patient (mean = 2.5 cycles). The maximum tolerated dose (MTD) was determined to be 900 mg/m^2, which was administered to a total of 6 patients. The safety, dose tolerance, PK, and PD of IV CPX-POM, administered at the MTD over 20 minutes are currently being characterized in an expansion cohort of 12 patients with muscle invasive bladder cancer scheduled for cystectomy.

CPX-POM was well tolerated up to the MTD of 900 mg/m^2. At the MTD, all of the related adverse events (AEs) were Grade 1 in severity. Nausea and vomiting were the most frequently reported treatment-emergent adverse events (TEAEs), reported by 6 and 8 patients, respectively, and were more common in the higher dose cohorts. The primary dose limiting toxicity was central nervous system (CNS)-related side effects, in particular a drug-related serious adverse event (SAE) of Grade 3 confusion in the 1200 mg/m^2 cohort, which was considered a dose limiting toxicity, and 4 AEs of Grade 1 confusion in the 600 and 900 mg/m^2 cohorts (i.e., 2 reports in each cohort). In the Nervous System system organ class (SOC), amnesia, dizziness, headache, and somnolence were also reported by 2 patients each. One patient in the 30 mg/m^2 dose cohort died during the study as a result of an SAE of pneumonia, which started on Study Day 28 and was considered not related to CPX-POM treatment.

During the Study CPX-POM-001 Dose Escalation Cohorts, CPX-POM injections were completed over a 10-minute period. During the present study, injections will be completed over a 20-minute period. Slowing the speed of CPX-POM injection may reduce the frequency and severity of CNS-related side effects such as confusion and infusion-related reactions.

There was no evidence of corrected QT interval (QTc) prolongation or other ECG abnormalities in any patient receiving CPX-POM doses up to 1200 mg/m^2.

CPX-POM was rapidly and completely metabolized to CPX. Plasma CPX-POM concentrations were observed in patients, however, concentrations declined rapidly, falling below the lower limits of the assay within 2 hours. CPX-POM was not detected in urine. Analysis of PK data showed that systemic exposure to CPX increased proportionately with increasing dose. The apparent elimination half-life of CPX typically ranged from 2 to 6 hours across the dose range studied. There was relatively low overall variability (<30%) in systemic clearance among individual patients. There was no indication of accumulation over the 5 days of CPX-POM dosing (mean area under the concentration-time curve at steady state (AUC_{ss})/initial area under the concentration-time curve (AUC_i) = 1.03). At the MTD, approximately 8.5% of the CPX-POM dose was excreted as CPX. The mean urine concentrations of CPX over 24 hours were >200 µM at the MTD.

2.2. Background on Bladder Cancer and Rationale for the Study

The purpose of this study is to characterize the safety and 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.

Bladder cancer is the sixth most common solid tumor in the United States with an estimated 80, 479 new cases and 17,670 deaths in 2019 (American Cancer Society, 2019). In 2016, there were an estimated 699,450 people living with this disease in the United States (Siegel et al, 2019). The disease has a high risk of recurrence as well as progression, thus requiring

life-long surveillance, making bladder cancer one of the most expensive cancers to treat on a per-patient-lifetime-basis (Botteman et al, 2003; Yeung et al, 2014). While the overall 5-year survival rate for bladder cancer is 77%, in those with advanced disease, this rate can be as low as 4% (NCI SEER Cancer Stat Facts, 2019).

Bladder cancer is defined as two diseases, each with different treatment approaches as well as outcomes. Seventy percent or more of newly diagnosed patients have non-muscle invasive bladder cancer (NMIBC) which is generally considered less life-threatening than muscle invasive bladder cancer (MIBC) (Heney, 1992). However, in spite of endoscopic resection followed by intravesical immunotherapy (Bacillus Calmette-Guérin [BCG]) or chemotherapy (e.g., mitomycin C, gemcitabine), 60 to 70% of those with NMIBC will recur and 20 to 30% will progress to MIBC (Aldoursari and Kassouf, 2010), where the gold standard treatment is radical cystectomy (RC) coupled with cisplatin-based chemotherapy in either neoadjuvant or adjuvant settings (Milan-Rodriguez et al, 2000). It is estimated, however, that as many as 40 to 50% of MIBC patients are ineligible for cisplatin chemotherapy due to impaired renal function (Dash et al, 2006). Patients with impaired performance status (Eastern Cooperative Oncology Group [ECOG] >1), heart failure (New York Heart Association [NYHA] class ≥III), grade ≥2 hearing loss, and/or grade ≥2 neuropathy are also ineligible for cisplatin-based chemotherapy. Given the poor complete response rate associated with neoadjuvant carboplatin and gemcitabine (Peyton et al, 2018), cisplatin-ineligible MIBC patients go straight to RC or enroll in clinical trials.

CPX, the active metabolite of CPX-POM, has been shown to be active against both MIBC and NMIBC in vitro. In vivo, CPX-POM treatment of mice with established bladder tumors induced by N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) resulted in robust antitumor activity. More importantly, CPX has been shown to have inhibitory activity against the Notch signaling pathway. Notch overexpression is associated with bladder cancer cell growth and survival. Inhibition of Notch may be an important target for the control of bladder cancers. Finally, currently available agents are administered topically by intravesical administration. Approximately 50% of NMIBC cases will recur within 12 months and 25% will progress to MIBC. CPX-POM affords an opportunity to develop a targeted, systemically administered therapy for NMIBC patients who are at risk of progressing to MIBC as well as a neoadjuvant treatment for MIBC in cisplatin-ineligible patients.

CPX-POM potentially has several major advantages over CPX and CPX-O in the context of treatment for bladder cancer: 1) CPX-POM represents a composition of matter patentable invention; 2) CPX-POM possesses much improved physical and chemical properties that enable injectable formulation development; 3) by developing an injectable formulation of CPX-POM, CicloMed hopes to avoid the dose-limiting gastrointestinal toxicities and poor oral bioavailability observed following oral CPX-O administration; 4) CPX-POM is rapidly metabolized to CPX, which is eliminated in the urine as a glucuronide conjugate; 5) elevated beta-glucuronidase activity in the urine of bladder cancer patients has the potential to

hydrolyze the conjugate back to CPX and thereby affords the potential to target CPX to the bladder epithelium; and 6) CPX-POM administered systemically has the potential to deliver drug to the entire urinary tract (i.e., to treat upper urinary tract disease), as opposed to agents delivered by bladder instillation.

The Investigator's Brochure provides further details of the nonclinical studies and published clinical evaluations of CPX-POM (CPX-POM Investigator's Brochure, 2019).

3. OBJECTIVES

The primary objective 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 transurethral resection of a bladder tumor (TURBT)

The secondary objectives are:

- To determine the number of patients with treatment-related AEs
- To elucidate mechanisms of CPX-POM action on bladder tumor tissues employing 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

The exploratory objective is:

- To determine urine ß-glucuronidase activity

4. STUDY DESIGN

4.1. Overall Design

This will be an open-label study to determine the safety, dose tolerance, PK, and PD 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.

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

4.2. Rationale for Study Design

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 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 TURBT, and therefore will not need to undergo additional, study-specific, invasive procedures.

4.3. Dose Selection

The dose planned for administration to patients in this study is the MTD and RP2D that was determined during Study CPX-POM-001: 900 mg/m^2 once daily by 20 minute IV infusion for 5 days.

4.4. End of Study Definition

A patient is considered to have completed the study if he/she has completed 5 days of dosing with CPX-POM and has undergone TURBT from which tissue, blood, and urine samples are collected. Patients will also complete a Day 35 Follow-Up Visit.

The end of the study is defined as the date of the last procedure for the last patient in the study.

5. STUDY POPULATION

5.1. Inclusion Criteria

1. Patient is male or female aged ≥18 years.

2. Patient provided signed and dated informed consent prior to initiation of any study procedures.

3. Patient is likely to have a new bladder tumor based on clinical presentation or is at high risk for tumor recurrence based on previous history.

4. Patient has a cystoscopically confirmed bladder tumor and will be scheduled to undergo TURBT.

5. Patient has not received prior treatment for bladder cancer or completed their last intravesical therapy >6 months before screening.

6. Patient has an ECOG performance status of 0 (fully active, able to carry out all pre-disease activities without restriction) or 1 (unable to perform physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature).

7. Patient has a predicted life expectancy of ≥3 months.

8. Patient has adequate renal function (creatinine ≤1.5 × the upper limit of the normal range (ULN) or an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m^2).

9. Patient has adequate hepatic function, as evidenced by a total bilirubin ≤1.5 × ULN, aspartate aminotransferase (AST) ≤3 × ULN and /or alanine aminotransferase (ALT) ≤3 × ULN

10. Patient has adequate bone marrow function, as evidenced by hemoglobin ≥9.0 g/dL in the absence of transfusion within the previous 72 hours, platelet count ≥100×10^9cells/L, and absolute neutrophil count (ANC) ≥1.5×10^9 cells/L.

11. Patient has no significant ischemic heart disease or myocardial infarction within 6 months before the first dose of CPX-POM and currently has adequate cardiac function, as evidenced by a left ventricular ejection fraction of >50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); and corrected QT interval by Fridericia's correction formula (QTcF) <450 msec for males and <470 msec for females. The eligibility of patients with ventricular pacemakers for whom the QT interval may not be accurately measurable will be determined on a case-by-case basis by the Sponsor in consultation with the Medical Monitor.

12. Patient and his/her partner agree to use adequate contraception after providing written informed consent through 3 months after the last dose of CPX-POM, as follows:

    a. For women: Negative pregnancy test during Screening and at Day 1 of each treatment cycle and compliant with a medically-approved contraceptive regimen during and for 3 months after the treatment period or documented to be surgically sterile or postmenopausal.

    b. For men: Compliant with a medically-approved contraceptive regimen during and for 3 months after the treatment period or documented to be surgically sterile. Men whose sexual partners are of child-bearing potential must agree to use 2 methods of contraception prior to study entry, during the study, and for 3 months after the treatment period.

13. Patient is willing and able to participate in the study and comply with all study requirements.

5.2. Exclusion Criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1. Patients received prior intravesical therapy for bladder cancer within ≤6 months of the current diagnosis.
2. Patients must not have had any of the following within 6 months before study drug administration:

    a. Myocardial infarction

    b. Severe/unstable angina

    c. Symptomatic congestive heart failure

    d. Cerebrovascular accident or transient ischemic attack, or

    e. Pulmonary embolism

3. Ongoing cardiac dysrhythmias of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 grade 2.

4. Evidence of NYHA functional class III or IV heart disease.

5. Uncontrolled hypertension (>150/100 mmHg despite optimal medical therapy).

6. Patient has an uncontrolled or severe intercurrent medical condition. The decision to exclude a patient from the study for an uncontrolled or severe intercurrent medical condition will be made by the Principal Investigator. Examples could include epilepsy, resistant infection, or any other neurological disease that would make clinical assessment difficult.

7. Patient underwent major surgery or radiation therapy within 4 weeks before the first dose of CPX-POM or received an investigational drug or device within 4 weeks or 5 half-lives of that agent (whichever is shorter) before the first dose of CPX-POM. A minimum of 10 days between termination of the investigational drug and administration of CPX-POM is required.

8. If female, patient is pregnant or breast-feeding.

9. Patient has evidence of a serious active infection (e.g., infection requiring treatment with IV antibiotics).

10. Patient has a known, active Hepatitis A infection.

11. Patient has known human immunodeficiency virus (HIV) or Hepatitis B, or C infection, as such patients may be at increased risk for toxicity due to concomitant treatment and disease-related symptoms may preclude accurate assessment of the safety of CPX-POM.

12. Patient has an important medical illness or abnormal laboratory finding that, in the Investigator's opinion, would increase the risk of participating in this study.

13. Patient is taking warfarin.

14. Patients may not have another malignancy that could interfere with the evaluation of safety or efficacy of the study drug. Patients with a prior malignancy will be allowed without approval in the following circumstances:
    a. Not currently active and diagnosed at least 3 years prior to the date of registration.
    b. Non-invasive diseases such as low risk cervical cancer or any cancer in situ.
    c. Localized (early stage) cancer treated with curative intent (without evidence of recurrence and intent for further therapy), and in which no chemotherapy was indicated.(e.g., low/intermediate risk prostate cancer, etc.).
    d. NMIBC for which treatment was completed >6 months before the current diagnosis.
15. Patient has known allergy or hypersensitivity to any component of CPX-POM.
16. Patient is taking any iron replacement therapy administered IV, intramuscularly, or orally due to the potential for loss of anticancer activity due to drug and/or metabolites chelating iron.

5.3. Meals and Dietary Considerations

There are no meal or dietary restrictions.

5.4. Screen Failures

Patients who fail inclusion and/or exclusion criteria may not be rescreened for the study.

6. TREATMENTS

6.1. Investigational Product

6.1.1. Description of Investigational Product

Fosciclopirox or ciclopirox prodrug (CPX-POM), sodium ((6-cyclohexyl-4-methyl-2-oxopyridin-1(2H)-yl) oxy) methyl phosphate, is the phosphoryloxymethyl ester of CPX. CPX-POM will be provided as a sterile liquid formulation for IV administration.

6.1.2. Packaging and Labeling

CPX-POM will be packaged in plastic, 10-mL vials containing CPX-POM 50 mg/mL solution. Vials will be labeled according to applicable regulatory requirements.

6.1.3. Storage and Handling

CPX-POM vials must be stored under refrigerated conditions at 2 to 8 ºC.

Only patients enrolled in the study may receive CPX-POM and only authorized site staff may supply or administer CPX-POM. All CPX-POM must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

6.1.4. Dosage and Administration

At baseline, the body surface area (BSA) will be calculated by the Dubois method using Screening height and baseline weight measurements. The baseline BSA is to be used to determine the patient's study drug dose.

Dubois Formula: BSA= $\boldsymbol{0.007184 \times W^{0.425} \times H^{0.725}}$

CPX-POM will be administered as an IV infusion once daily on Days 1-5 of the study. CPX-POM will be added to a 100-mL piggyback bag of 0.9% sodium chloride solution and infused over a 20-minute period. The dose administered will be 900 mg/m^2.

6.1.5. Dose Modifications

Dose modifications are discouraged. However, if a patient develops an SAE that the Investigator believes may be mitigated by a dose modification, the Medical Monitor should be contacted to discuss the possibility of a dose modification.

6.1.6. Compliance

Administration of CPX-POM will be performed by site personnel. Compliance will be assessed by inspection of drug accountability records at the study site.

6.1.7. Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, placebos, and comparators. This includes acknowledgment of receipt of each shipment of investigational product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from CicloMed and quantities administered to patients, including lot number, date dispensed/administered, patient identifier number, and the initials of the person dispensing/administering the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with CicloMed requirements. Drug may be returned or destroyed on an ongoing basis during the study, if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet CicloMed's requirements for disposal, arrangements will be made between the site and CicloMed or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Further guidance and information for the final disposition of unused investigational product is provided in the Study Procedures Manual.

6.2. Prior and Concomitant Medications

Medications taken within 30 days before baseline (Study Visit 2) must be recorded as prior medications.

Prohibited concomitant medications include any anti-cancer agents, steroids, any iron replacement therapy, warfarin, or any drug known to have significant nephrotoxicity. A minimum of 10 days between termination of the prohibited concomitant medications or a duration of five elimination half-lives will be required prior to administration of IV CPX-POM to eligible patients. Concomitant radiation therapy is also prohibited.

Note that anti-emetics such as ondansetron or granisetron are allowed if used with caution and attention to the approved labelling.

All concomitant medications will be recorded from the time of Screening up to the time of TURBT. Routine medications associated with the cystectomy procedure do not need to be recorded. Starting at the time of TURBT, only medications associated with an AE related to CPX-POM treatment need to be recorded.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

In the event of discontinuation of CPX-POM, every effort should be made to complete the assessments that are scheduled for the Follow-up/Early Termination visit. See the Schedule of Assessments (Table 1) for data to be collected at the time of early termination.

7.2. Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The patient will be withdrawn before any CPX-POM treatment is administered if the in-office cystoscopy fails to confirm bladder tumor.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If a patient withdraws prematurely from the trial for any reason, study staff should make every effort to complete the full set of evaluations scheduled for the Follow-up/Early Termination visit. See the Schedule of Assessments (Table 1) for data to be collected at the time of early termination.

7.3. Lost to Follow Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if

necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS

8.1. Safety Assessments

8.1.1. Adverse Events and Serious Adverse Events

8.1.1.1. Definitions

Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g., such as venipuncture, biopsy) during or after Screening (before the administration of study investigational medicinal product).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.
- Complications and termination of pregnancy (see Section 8.1.2 for additional information)
- All AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- If progression of underlying malignancy is clearly consistent with the suspected progression of the underlying cancer as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or with clinical symptoms (clinical progression), it should not be reported as an AE/SAE. Similarly, hospitalization due exclusively to the progression of underlying malignancy should NOT be reported as an SAE.

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history case report form (CRF).
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy may be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An **SAE** is defined as any untoward medial occurrence that, at any dose:

- Results in death
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity. The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product.
- Other situations. Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of important medical events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.1.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) through the Follow-up visit (28 +/- 5 days after the last dose of study drug).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.1.1.3. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.1.1.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (within 24 hours from the first time a site team member is made aware of the event) by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.1.1.5. Reporting Procedures

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF.

It is not acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by CicloMed or its designee. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

All SAEs will be recorded and reported to the Sponsor or their designee within 24 hours from the time any site team member is made aware of the event. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. If any part of the source providing details of the event is not available, the Investigator will submit the SAE with as much information as he/she has at the time of the reporting requirements.

Contacts and procedures for SAE reporting can be found in the Study Procedures Manual.

8.1.1.6. Assessment of Causality

The investigator is obligated to assess the relationship between CPX-POM and each occurrence of each AE/SAE as follows:

- There is a "reasonable possibility" of a relationship between the CPX-POM and the AE. This conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- There is not a "reasonable possibility" of a relationship between CPX-POM and the AE.

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or contract research organization (CRO). However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or CRO. The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The relationship to study procedures (e.g., invasive procedures such as venepuncture or biopsy) should also be assessed using the following considerations:

- There is a reasonable possibility that the AE occurred as a result of protocol-mandated procedures such as venipuncture or biopsy.
- There is not a reasonable possibility that the AE occurred as a result of a protocol-mandated procedure.

8.1.1.7. Assessment of Intensity

The investigator will make an assessment of intensity (Grade) for each AE and SAE reported during the study, using as a guide the NCI CTCAE, as provided in the Study Procedures Manual.

8.1.1.8. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by CicloMed or its designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide CicloMed or its designee with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information. Contacts for SAE reporting can be found in the Study Procedures Manual.

8.1.2. Pregnancy

Pregnancies in female patients and female partners of male patients will be recorded from after the start of study intervention until 30 days after the last dose. All pregnancies must be followed to conclusion to determine outcomes for both mother and baby.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Sections 8.1.1.4 and 8.1.1.5. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

8.1.2.1. Male Patients with Partners who Become Pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive CPX-POM.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.1.2.2. Female Patients who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy. The

patient will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Any female patient who becomes pregnant while participating in the study will discontinue CPX-POM and be withdrawn from the study.

8.1.3. Other Safety and Screening Assessments

8.1.3.1. In-Office Cystoscopy and Cold Cup Biopsy

Patients will sign the informed consent prior to undergoing the in-office cystoscopy and cold cup biopsy procedures. These procedures will be performed according to the standard of care at the study site. Confirmed bladder tumor is required for continued study participation. In the unlikely event that a bladder tumor is not confirmed at the in-office cystoscopy, the patient will be withdrawn from the study. Tumor tissue will be provided for study evaluation as described in Section 8.3.

8.1.3.2. Cardiac Evaluation

Patients will undergo a cardiac evaluation at Screening using MUGA or ECHO to evaluate their eligibility to participate in the study.

Patients will also undergo a chest X-ray or computed tomography (CT) scan to confirm normal cardiac appearance/heart size at Screening.

8.1.3.3. Eastern Cooperative Oncology Group Performance Status

Patients will be evaluated for ECOG performance status at Screening and Follow-Up to evaluate their eligibility to participate in the study. The ECOG performance status grades and criteria are shown in Table 2.

Table 2. Eastern Cooperative Oncology Group Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

8.1.3.4. Physical Examinations

A complete physical examination will be conducted at Screening and Follow-up. At each other study visit, patients will be assessed for continued dosing and any possible symptoms/toxicities and a physical examination may be performed, if indicated (see Schedules of Assessments, Table 1). Body weight should be measured at each study visit. Height should be measured at Screening.

8.1.3.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, and temperature and will be measured at the times and days shown in the Schedules of Assessments (Table 1).

Vital signs will be measured before any blood draws or injections scheduled for the same time point.

8.1.3.6. Electrocardiograms

At Screening, 12-lead ECGs will be performed in triplicate, with each measurement separated by 2 minutes. The average of the 3 screening ECGs will be used to calculate QTc and QTcF (Fridericia's formula): $$\mathbf{QTc} = \frac{\mathbf{QT}}{\sqrt[3]{\mathbf{RR}}}$$

to determine study eligibility. Thereafter, single 12-lead ECGs will be performed at the dates and times indicated in the Schedules of Assessments (Table 1).

8.1.3.7. Clinical Laboratory Assessments

All protocol-required laboratory assessments, including hematology (including complete blood count), clinical chemistry (including comprehensive metabolic panel), and urinalysis must be conducted in accordance with the Study Procedures Manual and the Schedules of Assessments (Table 1).

Abnormal laboratory tests that are clinically significant should also be recorded as AEs on the CRF, or as medical history if noted during Screening.

A listing of clinical laboratory tests to be performed is provided in Table 3.

Table 3. Listing of Required Screening and Safety Laboratory Parameters

Laboratory Assessments	Parameters		
Hematology (CBC with differential)	• Hemoglobin • Hematocrit • Platelet count • RBC count • Reticulocytes	*WBC Count with Differential* • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
Clinical Chemistry (including CMP)	• Potassium • Sodium • Chloride • Glucose • BUN • Creatinine • Creatinine clearance	• ALT • AST • GGT • Alkaline phosphatase • Direct bilirubin • Indirect bilirubin • Total bilirubin	• Total protein • Albumin • Calcium • Bicarbonate • Magnesium • Phosphate • Lipase • Amylase
Routine Urinalysis	• Color • Turbidity • pH • Specific gravity • Glucose • Ketones	• Nitrites • Bilirubin • Urobilirubin • Protein • RBCs • WBCs	• Epithelial cells • Casts • Crystals • Bacteria • eGFR (Screening only)
Other	Serum or urine hCG pregnancy test (for women of child bearing potential)		

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CMP = comprehensive metabolic panel; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyltransferase; hCG = human chorionic gonadotropin; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell.

8.2. Pharmacokinetic Assessments

As shown in the Study Procedures Manual and the Schedule of Assessments (Table 1), a single blood (plasma) sample and a single clean-catch urine sample will be collected on Day 1 prior to drug administration. At the time of TURBT on Day 5, a single blood (plasma) and urine sample will be collected. Tissue, plasma, and urine concentrations of CPX-POM, CPX, and CPX-G will be determined employing Good Laboratory Practices (GLP)-validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Urine β-glucuronidase activity will be determined in the urine samples collected on Days 1 and 5 by enzyme linked immunosorbent assay (ELISA).

The actual date and time of each tissue, blood, and urine sample collection, and the date and time of the previous dose of CPX-POM will be recorded. Processing, storage, and shipping procedures are provided in the Study Procedures Manual.

8.3. Pharmacodynamic Assessments

Bladder tumor tissues obtained at diagnosis and TURBT will be evaluated by RNA-seq and ChIP-seq analyses to elucidate mechanisms of CPX-POM action on bladder tumor tissues. Immunohistochemical analysis of prepared paraffin-embedded bladder tumor slides will be performed to determine cell proliferation, Notch and Wnt cell signaling pathways, as well as bladder tumor tissue CD8+ TIL.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be developed and finalized before database lock and will describe the finalized plans for analysis of study data. This section is a summary of the planned statistical analyses at the time of protocol development.

9.1. Number of Patients

The estimated number of patients is 12.

9.2. Analysis Sets

9.2.1. Safety

The **Safety Set** will consist of all patients who receive at least 1 dose of study drug. All safety and PD data will be analyzed using the safety set.

9.2.2. Pharmacokinetics

The **Pharmacokinetic Set** will consist of all patients for whom a tissue, plasma, and/or urine sample is obtained and analyzed for determination of plasma drug and metabolites concentration.

9.3. Data Handling Conventions

9.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

9.5. Safety Analysis

Safety data will be presented in by-patient listings. Categorical safety endpoints will be summarized by frequency of events/abnormalities for each dose group and overall. Continuous safety endpoints will be summarized using descriptive statistics (n, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], minimum, maximum) for each dose group and overall.

9.5.1. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). SOC, High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term, and Lower-Level Term (LLT) will be attached to the clinical database.

AEs will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of CPX-POM.

Summaries (number and percentage of patients) of treatment-emergent AEs (by SOC, and Preferred Term) will be provided by dose group/cohort and overall.

9.5.2. Laboratory Evaluations

Summaries of clinical laboratory data will be provided using descriptive statistics. No inferential statistics will be provided. Quantitative values and change from baseline in quantitative values will be summarized by dose group. Listings of all laboratory results and reference ranges will be provided.

Graded laboratory abnormalities will be defined using the grading scheme based on NCI CTCAE (4.03). 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 treatment group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent.

9.5.3. Other Safety Evaluations

Physical examination, ECG, and vital signs data will be summarized by dose group and overall. Concomitant medications will be coded using the World Health Organization Drug Dictionary and listed by dose group.

9.6. Pharmacokinetic Analysis

Tissue, plasma, and urine concentrations of CPX-POM and its metabolites will be determined by GLP-validated liquid chromatography tandem mass spectroscopy 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.

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.

9.7. Pharmacodynamic Analyses

Bladder tumor tissues will be analyzed using RNA-seq and ChIP-seq 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.

9.8. Interim Analyses

No formal interim analysis is planned.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

10.1.1. Institutional Review Board/Ethics Committee

IRBs must be constituted according to the applicable state and federal requirements of each participating location including International Council on Harmonisation (ICH) Good Clinical Practice (GCP).

It is the responsibility of each investigational site to submit the protocol, IB, patient ICF, patient recruitment materials (if applicable), and other documentation as required by the IRB to their IRB for review and approval. A copy of the written approval must be provided to the sponsor or CRO. The documentation should clearly mention the approval/favorable opinion of the protocol, the patient ICF, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRB(s) and provided to the sponsor or CRO prior to the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

Sites must adhere to all requirements stipulated by their respective IRB. This includes notification to the IRB regarding: protocol amendments, updates to the patient informed consent, recruitment materials intended for viewing by patients, IND safety reports, serious and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of final study reports and summaries to IRB.

It is the responsibility of each investigational site to submit information to the appropriate IRB for annual review and annual re-approval.

10.1.2. Ethical Conduct of the Study

This study will be conducted according to the protocol, Code of Federal Regulations (21 CFR Parts 50, 54, 56, and 312), the Declaration of Helsinki, and ICH GCP. Each investigator will conduct the trial according to applicable local or regional regulatory requirements.

10.1.3. Informed Consent

Prior to any study procedures being performed, patients and the person conducting the consent discussion will be required to sign and date the IRB-approved ICF, and each patient will be given a copy. In addition, this information should be recorded in the patient's medical record (i.e., source document).

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki, the Code of Federal Regulations (21 CFR Part 50.25), the ICH GCP guidelines, and in accordance with any local regulations. The investigator is responsible for the preparation, content, and IRB approval of the informed consent. The ICF must be approved by the site-designated IRB and be acceptable to the sponsor or CRO.

The ICF must be written in a language fully comprehensible to the prospective patient. The investigator or designee shall give the patient adequate opportunity to read the ICF before it is signed and dated. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. Patients must be given ample opportunity to inquire about details of the study.

10.1.4. Confidentiality

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties.

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
NOTE: The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

The investigator agrees that all information received from CicloMed, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of CicloMed during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from CicloMed. The investigator further agrees to take all

reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.2. Study Oversight

10.2.1. Data Quality Assurance

All patient data relating to the study will be recorded in a printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.2.2. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Study Procedures Manual.

10.2.3. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed on a rolling basis upon database lock for each site individually or as the Sponsor determines.

A study site is considered closed when all required documents, study supplies, and investigational product have been collected and/or destroyed, and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further CPX-POM development

10.2.4. Reporting of Results and Publications

CicloMed will fulfill its commitment to publicly disclose the results of this study through posting the results on the www.clinicaltrials.gov web site.

A clinical study report will be prepared and provided to the regulatory agency(ies). CicloMed will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Any investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with CicloMed’s request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data includes at least the following information for each patient:

- patient identification (name, date of birth, gender);
- documentation that patient meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- participation in trial (including trial number);
- trial discussed and date of informed consent;
- dates of all visits;
- documentation that protocol specific procedures were performed;
- results of efficacy parameters, as required by the protocol;
- start and end date (including dose regimen) of trial medication;
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);
- concomitant medication (including start and end date, dose if relevant; dose changes should be motivated);
- date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with CicloMed. The investigator must notify CicloMed before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, CicloMed must be notified in advance (i.e. in the case of a Principal

Investigator moving to a new location, retiring, etc.). If a study site is assigned to another investigator for archival oversight or if the files are to be moved, this change will be noted in a memo, the Sponsor will be contacted, and the IRB will be notified depending on the IRB requirements.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and CicloMed to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the sponsor for a period up to 2 years for purposes of this study.

10.2.6. Case Report Forms

For each patient enrolled, a CRF must be completed and signed by the Principal Investigator or sub-investigator (as appropriate) within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a screening period if a CRF was initiated). If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

10.2.7. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from CicloMed or its representatives, to IRBs, or to regulatory authority or health authority inspectors.

10.2.8. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2.9. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs. In terminating the study, CicloMed and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

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