CicloMed LLC

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1, First-in-Human, Safety, Dose Tolerance, Pharmacokinetics, and Pharmacodynamics Study of CPX-POM in Patients with Advanced Solid Tumors
Sponsor:	CicloMed LLC 411 Nichols Rd. Suite 217 Kansas City, MO 64112
IND No.:	132545
clinicaltrials.gov Identifier:	NCT03348514
Indication:	Advanced Solid Tumors
Protocol ID:	CPX-POM-001
Protocol Versions/Dates:	Original Protocol Version 1.0 / 15 August 2017 Amendment 1, Version 2.0 / 19 September 2017 Amendment 2, Version 3.0 / 03 November 2017 Amendment 3, Version 4.0 / 04 January 2018 Amendment 4, Version 5.0 / 06 August 2018

SPONSOR SIGNATURE PAGE

CicloMed LLC
411 Nichols Rd.
Suite 217
Kansas City, MO 64112

A Phase 1, First-in-Human, Safety, Dose Tolerance, Pharmacokinetics, and Pharmacodynamics Study of CPX-POM in Patients with Advanced Solid Tumors

Amendment 4, Version 5.0, 06 August 2018.

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

[redacted] (Date)

[redacted] (Date)

INVESTIGATOR PROTOCOL AGREEMENT

A Phase 1, First-in-Human, Safety, Dose Tolerance, Pharmacokinetics, and Pharmacodynamics Study of CPX-POM in Patients with Advanced Solid Tumors

Amendment 4, Version 5.0, 06 August 2018

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 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

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1. Synopsis

CicloMed LLC
411 Nichols Rd.
Suite 217
Kansas City, MO 64112

Study Title:	A Phase 1, First-in-Human, Safety, Dose Tolerance, Pharmacokinetics, and Pharmacodynamics Study of CPX-POM in Patients with Advanced Solid Tumors
IND Number:	132545
Study Centers Planned:	Approximately 6 centers in the United States
Objectives:	The primary objective of this study is as follows: • To evaluate the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of ciclopirox phosphoryloxymethyl ester (CPX-POM) administered intravenously (IV) and establish the CPX-POM dose recommended for further investigation. The secondary objectives of this study are as follows: • To characterize the plasma and urine pharmacokinetics (PK) of CPX-POM and its metabolites following single and multiple dose administration; • To identify preliminary anti-tumor activity of CPX-POM; • To determine urine β-glucuronidase activity in patients participating in the trial. The exploratory objectives of this study are as follows: • To characterize the pharmacologic effects of CPX-POM on circulating biomarkers of Wnt and Notch cell signaling pathways; • To explore pharmacodynamic (PD) relationships between changes in circulating biomarkers and drug and/or metabolites exposure and other outcomes.
Study Design:	This is a first-in-human, Phase 1, multicenter, open label, dose escalation study to evaluate the DLTs and MTD and to determine the recommended Phase 2 dose (RP2D) of CPX-POM administered IV in patients with any histologically- or cytologically-confirmed solid tumor type. Secondary objectives include characterization of the safety and PK profile of CPX-POM and identification of preliminary anti-tumor activity in this patient population. Biomarkers and their relationship to PK and other outcomes will be examined as an exploratory objective. The study will initially employ an accelerated escalation design, with a single patient enrolled in each cohort (i.e., Single-Patient Cohorts). The initial patient cohort will receive CPX-POM at a starting dose of 30 mg/m^2. Doses will be escalated in 100% increments (i.e., doubling), until a ≥Grade 2 toxicity (with the exception of alopecia), as determined according to the United States (US)

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, is encountered, at which point that cohort and all subsequent cohorts will follow a classical "3 + 3" dose escalation design (i.e., Standard Dose Escalation Cohorts).

After each cohort is completed, a Safety Review Committee (SRC) comprised of the CRO Medical Monitor, Principal Investigator(s), and Sponsor representatives will meet to discuss the data and decide upon the next dose escalation. Doses in the standard cohorts will be escalated in 25 to 50% increments, based on SRC decision, until the MTD is reached. In addition, after completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated.

Intrapatient dose escalation will not be allowed in any patient at any time.

Each patient in a dose cohort must have received at least 80% of their CPX-POM doses, unless due to toxicity, during Cycle 1 with follow-up safety evaluations through Day 22 (or Cycle 2, Day 1, if continuing in the study) to be eligible for the assessment of DLT.

Patients may continue to receive cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies.

Approximately 24 patients will be enrolled in the Single-Patient and Standard Dose Escalation Cohorts to establish the MTD. In addition to these estimated 24 patients, Expansion Cohort(s) may be enrolled after the MTD is reached to either explore different dosing schedules, increase the experience with a particular tumor type (e.g., muscle invasive bladder cancer [MIBC]), or to examine the safety and anti-tumor activity of CPX-POM in combination with certain other anticancer agents.

Dose escalation procedures will be conducted as follows:

Accelerated Titration (Single-Patient Cohorts; n=1 each)

No ≥Grade 2 adverse events (AEs)	• Continue evaluation of single-patient dose cohorts. • Escalate by 100% to next dose level.
At least 1 ≥Grade 2 AE not meeting the definition of DLT	• Expand current and subsequent cohorts to at least 3 patients (see Standard Dose Escalation Scheme below).
1 DLT	• Expand current cohort up to 6 patients or until 2 DLTs are encountered (Standard Dose Escalation Scheme below).

Standard Dose Escalation (Standard Cohorts; n=3 to 6 each)

No DLT	• Escalate by 25−50% to next dose level.
1 DLT in ≤3 patients	• Expand cohort up to 6 patients.
1 DLT in 6 patients	• Escalate by 25−50% to next dose level.
> 1 DLT in ≤6 patients	• MTD reached; stop dose escalation. • Possibly explore intermediate doses for the RP2D.

	A Dose-Limiting Toxicity will be defined as any of the following if deemed related to study drug:
	• Grade 4 thrombocytopenia of any duration
	• Grade 3 thrombocytopenia with significant hemorrhage of any duration
	• Grade 4 absolute neutrophil count (ANC) >5 days
	• Febrile neutropenia
	• Grade ≥3 non-hematologic toxicity of any duration, <u>except:</u>
	  o Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours
	  o Grade 3 fatigue lasting <5 days
	  o Grade 3 hypertension that can be controlled with medical therapy
	  o An increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome
	  o Serum lipase and/or serum amylase CTCAE Grade 3 ≤7 consecutive days without clinical signs or symptoms of pancreatitis
	• Delay in study drug due to toxicity for >2 weeks
	• Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3xULN with bilirubin >2x the upper limit of normal (ULN) without another explanation (e.g., cholestasis)
	Any patient who is unable to receive 80% of the expected dose of CPX-POM (i.e., patients who are unable to receive at least 4 of the 5 scheduled doses) because of AEs will be considered to have a DLT.

Number of Patients Planned:	Approximately 24 patients will be enrolled in dose escalation cohorts to establish the MTD. In addition to these estimated 24 patients, Expansion Cohort(s) may also be enrolled after the MTD is reached.
Target Population:	Patients with any histologically- or cytologically-confirmed solid tumor type that is refractory to standard therapy. Patients should only be included if no therapy exists or if they have received all standard therapies that would be potentially curative or might provide significant benefit.
Duration of Study:	Patients who receive one treatment cycle will be in this study for up to approximately 8 weeks: up to a 28-day Screening period, a 21-day Treatment cycle, and a Follow-up period out to 28 ± 5-days after the last dose (i.e., approximately Day 33). After the first treatment cycle, patients may continue to receive cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies.

Diagnosis and Main Eligibility Criteria:	Patients eligible for enrollment in this study will be adults with any histologically- or cytologically-confirmed metastatic or advanced-stage solid tumor that is refractory to standard therapy. Patients should only be included if no therapy exists or if they have received all standard therapies that would be potentially curative or might provide significant benefit. Patients must have a life expectancy ≥3 months, an Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1, no significant ischemic heart disease, adequate hepatic function, and a baseline glomerular filtration rate (GFR) >50 mL/min/1.73m^2. Females must not be pregnant and, if of childbearing potential, must use an effective method of contraception to avoid pregnancy during and for 3 months after participation in the trial. Patients who have any risk factor for torsade de pointes or any uncontrolled or severe intercurrent medical condition, or who have had major surgery or prior systemic chemotherapy or radiation therapy within the previous 4 weeks are excluded.
Test Product, Dose, and Mode of Administration:	Escalating doses of CPX-POM will be administered by 10-minute IV infusion once daily on Days 1-5 of each 21-day cycle. After completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated (e.g., adding an additional 5 days of dosing to each treatment cycle). Patients may continue to receive cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies. The starting dose will be 30 mg/m^2.
Reference Therapy, Dose, and Mode of Administration:	Not applicable.
Criteria for Evaluation:	<u>Safety:</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. The MTD will be defined as the dose BELOW that dose which causes DLTs in ≥33% of patients. <u>Pharmacokinetics:</u> Serial blood (plasma) samples and complete urine will be collected over 24-hour periods starting after the first (Day 1) and fifth (Day 5) doses of CPX-POM during Cycle 1 to characterize single dose and steady-state plasma and urine PK of CPX-POM, ciclopirox (CPX), and ciclopirox glucuronide (CPX-G). If patients are unable or unwilling to attend the required 12 hours of clinic visitation required for steady-state PK sampling on Day 5 of Cycle 1, the steady-state PK sampling may be postponed to Day 5 of Cycle 2. Urine β-glucuronidase activity will be measured prior to and after 5 days of CPX-POM administration (i.e., on Days 1 and 5 of Cycle 1). <u>Pharmacodynamics:</u> Blood will be collected to characterize the effects of CPX-POM on circulating biomarkers of Wnt and Notch cell signaling pathways. Plasma and peripheral blood mononuclear cells (PBMCs) will be isolated from blood. Vascular

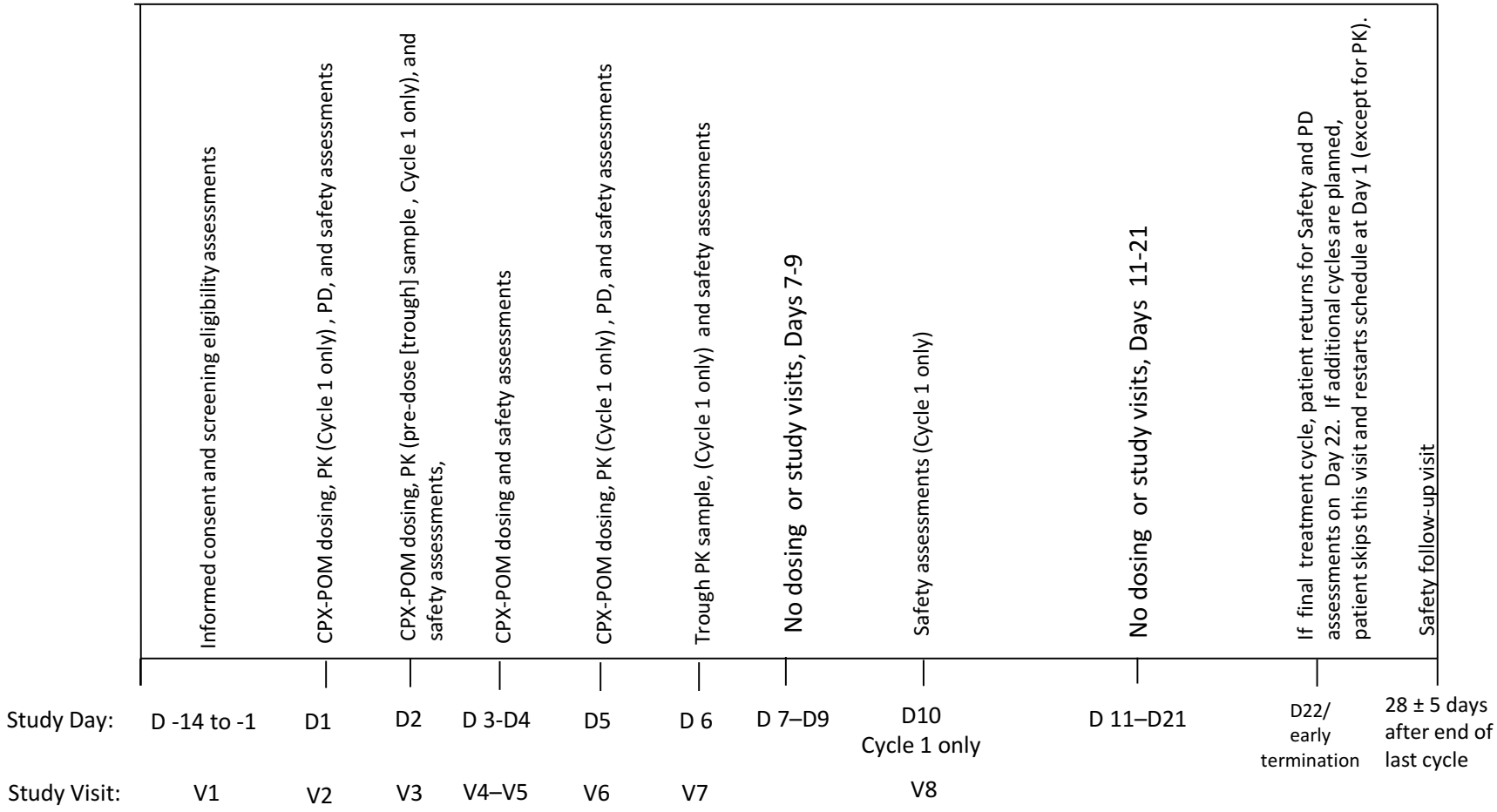
	endothelial growth factor (VEGF), interleukin (IL)-6, and IL-8 concentrations will be measured in plasma by enzyme-linked immunoassay (ELISA). Quantitative real-time polymerase chain reaction (qRT-PCR) will be used to characterize gene expression of circulating biomarkers of Wnt and Notch signaling pathways in PBMCs.
Statistical Methods:	Safety: 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: Standard PK parameters will be derived from resultant plasma and urine drug and metabolite concentration-time data using non-parametric methods. PK parameters will be summarized using descriptive statistics. Pharmacodynamics: A logistic regression will be used to estimate the predicted toxicity probability at each dose level. Relationships between dose, drug and metabolite exposure, PD response, and other endpoints (i.e., ECGs, toxicity, safety, and biomarker endpoints) may be explored using descriptive statistics, and/or additional PK/PD modeling.

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: CPX-POM = ciclopirox phosphoryloxymethyl ester; D = day; PD = pharmacodynamic; PK = pharmacokinetic; 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 [5]
Study Days:	D -28 to D -1	D1 [1]	D2	D3	D4	D5 [1]	D6	D10 [2] (Cycle 1 only)	D22 (last cycle) [4]	28 (±5) days post last dose or at early termination
Study Visits:	V1	V2	V3	V4	V5	V6	V7	V8		
Informed consent	X									
Inclusion/exclusion criteria	X	X								
ECOG Performance Status	X									X
Medical history	X									
HIV and hepatitis screening [6]	X									
Pregnancy test [7]	X	X								
Cancer evaluation [8]	X	X								
CT or MRI	X									
MUGA or ECHO	X									
Hematology [9]	X	X			X			X	X	X
Clinical chemistry [10]	X	X			X			X	X	X
Thyroid panel [11]	X	X								
Coagulation test [12]	X	X								
Urinalysis [13]	X	X				X		X	X	X
Full physical exam [14]	X									X
Assess for physical symptoms/toxicities [15]		X	X	X	X	X	X	X	X	
Ophthalmologic exam [15]	X									X
Vital signs [16]	X	X	X	X	X	X	X	X	X	X
ECG [17]	X	X				X				X
Start 24- hour Holter monitor [18]		X								

Study Procedure	Screening Period	Treatment Period								Follow-up Period [5]
Study Days:	D -28 to D -1	D1 [1]	D2	D3	D4	D5 [1]	D6	D10 [2] (Cycle 1 only)	D22 (last cycle) [4]	28 (±5) days post last dose or at early termination
Study Visits:	V1	V2	V3	V4	V5	V6	V7	V8		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
PK blood samples [19]		X	X			X	X			
PK urine samples [20]		X	X			X	X			
β glucuronidase urine sample [21]		X				X				
Biomarker blood sample [22]		X				X			X	X
Body surface area [23]		X								
CPX-POM infusions [24]		X	X	X	X	X				

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BSA = body surface area; BUN = blood urea nitrogen; 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; GGT = gamma glutamyl transferase; HIV = human immunodeficiency virus; IV = intravenous; MUGA = multi-gated acquisition; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; V = visit; WBC = white blood cell.

1. On Days 1 and 5 of Cycle 1, patients will be required to stay at the clinical research unit for at least 12 hours for PK sampling and other assessments. If patients are unable or unwilling to attend the required 12 hours of clinic visitation required for steady-state PK sampling on Day 5 of Cycle 1, the steady-state PK sampling may be postponed to Day 5 of Cycle 2. To shorten the duration of the Cycle 1, Day 1 visit, if needed, the safety laboratory blood samples required for this visit may be drawn up to 3 days before Day 1.
2. The Day 10 (Visit 8) study visit will only be required during Cycle 1.
3. After cycle 1; visit windows can be considered on a case by case basis due to events such as holidays; Cycle 1 needs to occur without visit windows. D6 can occur +2 calendar days for cycles after Cycle 1 is completed.
4. If final treatment cycle, patient returns for assessments on Day 22. If additional cycles are planned, patient skips this visit and restarts schedule at Day 1 (except for PK). Patients may continue to receive cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies.

5. The Follow-up visit will occur 28±5 days after the last dose of CPX-POM administered during the last treatment cycle. 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.
6. Hepatitis screening will include tests for Hepatitis A, Hepatitis B, and Hepatitis C.
7. Pregnancy tests will be required only for women of child bearing potential at Screening and before dosing on Day 1 of each treatment cycle. Urine or serum pregnancy tests are acceptable.
8. Cancer evaluation will include determination of staging and metastases for screening purposes (see Section 8.1). Disease response assessments will be performed for patients with measurable disease within 28 days prior to the first dose of CPX-POM and repeated at the end of every second cycle (i.e., at approximately 6-week intervals). During the Dose-Escalation Phase of the study, Screening cancer evaluations may be performed up to 28 days before Cycle 1, Day 1. For patients enrolled in any Expansion cohorts, Screening cancer evaluations must be performed within 28 days of Cycle 1, Day 1.
9. Hematology will include measurement of hemoglobin, hematocrit, platelets, RBC, reticulocytes, and WBC with differential. To shorten the duration of the Cycle 1, Day 1 visit, if needed, the safety laboratory blood samples required for this visit may be drawn up to 3 days before Day 1 (Cycle 1 only).
10. Clinical chemistry will include measurement of potassium, sodium, chloride, glucose, BUN, creatinine, creatinine clearance, ALT, AST, ALP, GGT, alkaline phosphatase, indirect bilirubin, direct bilirubin, total bilirubin, total protein, albumin, calcium, bicarbonate, magnesium, phosphate, lipase, and amylase. To shorten the duration of the Cycle 1, Day 1 visit, if needed, the safety laboratory blood samples required for this visit may be drawn up to 3 days before Day 1.
11. Thyroid panel will include TSH, free T4, and free and total T3 and will be repeated on D1 of each cycle.
12. Coagulation tests will include PT and aPTT and will be repeated on D1 of each cycle.
13. 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.
14. A full physical examination will be conducted at Screening and at 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.
15. Ophthalmology evaluations will be conducted at least on Day 1 and at Follow-up by a qualified ophthalmologist and will include visual acuity, pupil exam, confrontation visual field, extraocular motility and alignment, interior slit lamp examination, and dilated fundus examination of the retina. Additional ophthalmology evaluations may be performed at any other time, if indicated, as determined by the investigator.
16. 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. On Days 1 and 5, vital signs will be measured at pre-dose and at 6-hour intervals post-dose.
17. 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 of Cycle 1; on Day 1 of each subsequent treatment cycle; and at the Final Study visit.
18. **Cycle 1**: Starting on Day 1 of Cycle 1, digital Holter monitoring will be performed from 45 minutes pre-dose through 24 hours post-dose. ECG extractions of the continuous Holter recordings will be performed at 45, 30, and 15 minutes pre-dose and at specific post-dose time points

coinciding with the serial blood sampling time points for pharmacokinetics. Patients will be instructed to assume a supine position 5-10 minutes prior to each serial blood sampling time point and remain supine throughout the 5-minute ECG extraction period just prior to serial blood sample collection. During the 24-hour Holter monitoring period, a 12-lead ECG tracing may be printed out at any time while the patient is in the clinic at the discretion of the investigator. If for any reason Holter monitoring is not performed in conjunction with the PK sampling on Day 1 or the tracings are of poor quality, Holter monitoring may be performed in conjunction with the PK sampling on Day 5.

19. **Cycle 1:** Serial, 3-mL blood samples will be taken for determination of plasma CPX-POM and metabolites concentrations during Cycle 1 at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours following completion of the 10-minute IV infusion on Day 1 and on Day 5. Each PK sample should be collected as close as possible to the planned time. The 12.0 hour collection can have a +/- 1-hour window (collect within 11 to 13 hours) and the exact time must be recorded. The actual date and time of each blood sample collection will be accurately recorded.
20. **Cycle 1:** Complete 24-hour urine samples for determination of CPX-POM and metabolites concentrations, and measurement of urine volume will be obtained from each patient in urine collection and storage containers during Cycle 1. A sample will be taken at pre-dose on Day 1, and complete urine samples will be collected at 0-12 and 12-24 hour collection intervals post-dose on Days 1 and 5. The 12 hour collection can have a +/- 1-hour window (collect within 11 to 13 hours) and the exact time must be recorded.
21. **Cycle 1:** Urine β-glucuronidase activity will be determined in the complete 24-hour urine samples collected on Day 1 and Day 5 of Cycle 1.
22. 7-mL blood samples will be obtained in EDTA-containing blood collection tubes at pre-dose on Day 1 and Day 5 of each treatment cycle, and on Day 22 of the last treatment cycle. Plasma and buffy coat (PBMCs) will be isolated, transferred to storage tubes, and stored frozen.
23. BSA will be calculated by the site personnel using the Dubois method of calculation using screening height and baseline weight measurements. BSA is to be recalculated before study drug administration on Day 1 of every other treatment cycle, starting with Cycle 3 and the patient's study drug dose adjusted accordingly.
24. CPX-POM infusions will be administered once every 24 hours as 10-minute IV infusions on Days 1-5 of each 21-day treatment cycle. After completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated (e.g., adding an additional 5 days of dosing to each treatment cycle).

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve following a single dose on Day 1
AUCss	area under the concentration-time curve over the dosing interval at steady-state following drug administration on Day 14
$AUC_{[0-t]}$	area under the concentration-time curve following administration of a single dose on Day 1
$AUC_{[t-\infty]}$	area under the concentration-time curve following administration of a single dose on Day 1 from the last quantifiable concentration (t) to infinity
AUC_{inf}	area under the curve from time zero to extrapolated infinite time [AUC(0 ∞)] following administration of a single dose on Day 1 as the sum of AUC[0-t] + AUC(t-∞)
BSA	body surface area
CLr	single dose (Day 1) and steady-state (Day 14) renal clearance
CLs	systemic clearance following administration of a single dose on Day 1
CLss	systemic clearance at steady-state
C_{max}	the maximum observed serum/plasma/PBMC concentration of drug
Css_{max}	the maximum observed plasma concentration of drug and metabolites observed at steady-state over the dosing interval
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
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunoassay

FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
HNSTD	highest non-serious toxic dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IL	Interleukin
IRB	institutional review board
IV	intravenous
LC-MS/MS	liquid chromatography tandem mass spectroscopy
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle invasive bladder cancer
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
n	number of subjects
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PK	pharmacokinetic
PT	prothrombin time
Q1	first quartile
Q3	third quartile
qRT-PCR	quantitative real-time polymerase chain reaction
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria for Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SOC	system organ class

SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
t_{max}	the time (observed time point) of C_{max}
tss_{max}	the time (observed time point) of C_{max}^{ss}
$t_{½}$	apparent elimination half-life
ULN	upper limit of the normal range
US	United States
Vd	apparent volume of distribution
VEGF	vascular endothelial growth factor
Vss	Steady-state volume of distribution
λ	apparent first-order elimination rate constant

2. INTRODUCTION

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).

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 starting dose of CPX-POM in patients was selected based on the results of the IV CPX-POM 28-day Good Laboratory Practices (GLP) toxicology studies conducted in the rat and dog and consistent with FDA guidance (FDA, 2010) (see Section 4.4).

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).

The Investigator's Brochure provides further details of the nonclinical studies and published clinical evaluations of CPX-POM (CPX-POM Investigator's Brochure, 2017).

3. OBJECTIVES

The primary objective of this study is:

- To evaluate the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of CPX-POM administered IV and establish the CPX-POM dose recommended for further investigation.

The secondary objectives of this study are:

- To characterize the plasma and urine PK of CPX-POM and its metabolites following single and multiple dose administration;
- To identify preliminary anti-tumor activity of CPX-POM;
- To determine urine β-glucuronidase activity in patients participating in the trial.

The exploratory objectives of this study are:

- To characterize the pharmacologic effects of CPX-POM on circulating biomarkers of Wnt and Notch cell signaling pathways;
- To explore PD relationships between changes in circulating biomarkers and drug and/or metabolites exposure and other outcomes.

4. STUDY DESIGN

4.1. Overall Design

This is a first-in-human, Phase 1, multicenter, open label, dose escalation study to evaluate the DLTs and MTD and to determine the recommended Phase 2 dose (RP2D) of CPX-POM administered IV in patients with any histologically- or cytologically-confirmed solid tumor type. Secondary objectives include characterization of the safety and PK profile of CPX-POM and identification of preliminary anti-tumor activity in this patient population. Biomarkers and their relationship to PK and other outcomes will be examined as an exploratory objective.

The study will initially employ an accelerated titration design, with a single patient enrolled in each cohort (i.e., Single-Patient Cohorts). The initial patient cohort will receive CPX-POM at a starting dose of 30 mg/m^2. Doses will be escalated in 100% increments (i.e., doubling), until a ≥Grade 2 toxicity (with the exception of alopecia), as determined according to the United States (US) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, is encountered, at which point that cohort and all subsequent cohorts will follow a classical "3 + 3" dose escalation design (i.e., standard cohorts).

After each cohort is completed, a Safety Review Committee (SRC) comprised of the CRO Medical Monitor, Principal Investigator(s), and Sponsor representatives will meet to discuss the data and decide upon the next dose escalation. Doses in the standard cohorts will be escalated in 25 to 50% increments, based on SRC decision, until the MTD is reached. In addition, after completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated.

Intrapatient dose escalation will not be allowed in any patient at any time.

Each patient in a dose cohort must have received at least 80% of their CPX-POM doses, unless due to toxicity, during Cycle 1 with follow-up safety evaluations through Day 22 (or Cycle 2, Day 1, if continuing in the study) to be eligible for the assessment of DLT.

Patients may continue to receive cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies.

Approximately 24 patients will be enrolled in the Single-Patient and Standard Dose Escalation Cohorts to establish the MTD. In addition to these estimated 24 patients, Expansion Cohort(s) may be enrolled after the MTD is reached to either explore different dosing schedules, increase the experience with a particular tumor type (e.g., muscle invasive

bladder cancer [MIBC]), or to examine the safety and anti-tumor activity of CPX-POM in combination with certain other anticancer agents.

All patients are to attend a Follow-up Visit 28 days (± 5 days) after the last study drug dose. No follow-up after completion of the Follow-up Visit is planned, with the exception of monitoring of ongoing treatment-emergent adverse events (AEs) until resolution or until the AE is clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Dose escalation procedures will be conducted as shown in Table 2. For further details and example doses, see Section 4.2.

Table 2. Dose Escalation Procedures

Accelerated Titration (Single-Patient Cohorts; n=1 each)	
No ≥Grade 2 AEs	• Continue evaluation of single-patient dose cohorts. • Escalate by 100% to next dose level.
At least 1 ≥Grade 2 AE not meeting the definition of DLT	• Expand current and subsequent cohorts to at least 3 patients (see Standard Dose Escalation Scheme below).
1 DLT	• Expand current cohort up to 6 patients or until 2 DLTs are encountered (Standard Dose Escalation Scheme below).
Standard Dose Escalation (Standard Cohorts; n=3 to 6 each)	
No DLT	• Escalate by 25–50% to next dose level.
1 DLT in ≤3 patients	• Expand cohort up to 6 patients.
1 DLT in 6 patients	• Escalate by 25–50% to next dose level.
> 1 DLT in ≤ 6 patients	• MTD reached; stop dose escalation. • Possibly explore intermediate doses for the RP2D.

Abbreviations: AE = adverse event; DLT = dose limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose.

A Dose-Limiting Toxicity will be defined as any of the following, if deemed related to study drug:

- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia with significant hemorrhage of any duration
- Grade 4 absolute neutrophil count (ANC) greater than 5 days
- Febrile neutropenia
- Grade ≥3 non-hematologic toxicity of any duration, except:
    - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours
    - Grade 3 fatigue lasting <5 days
    - Grade 3 hypertension that can be controlled with medical therapy
    - An increase of indirect (unconjugated) bilirubin indicative of M. Meulengracht/Gilbert's syndrome
    - Serum lipase and/or serum amylase CTCAE Grade 3 ≤7 consecutive days without clinical signs or symptoms of pancreatitis
- Delay in study drug due to toxicity for >2 weeks
- alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3x the upper limit of normal (ULN) with bilirubin >2xULN without another explanation (e.g., cholestasis)
- Any patient who is unable to receive 80% of the expected doses of CPX-POM (i.e., patients who are unable to receive at least 4 of the 5 scheduled doses) in Cycle 1 because of AEs will be considered to have a DLT.

4.2. Planned Doses for Dose Escalation

As described in Sections 4.1, 4.4, and 6.1.4, the starting dose for this study will be 30 mg/m^2 as a 10-minute IV infusion once daily for 5 days, repeated every 21 days. As stated in Section 4.1, the study will initially adopt an accelerated titration design until ≥Grade 2 toxicity is encountered. Therefore, as an example, if the first ≥Grade 2 toxicity is not seen before the 120 mg/m^2 dose level in the early cohorts, then the doses shown in Table 3 may be administered.

Table 3. Example Doses for Accelerated Titration Cohorts

Cohort	Daily Dose (mg/m^2)	Number of Patients
1	30*	1
2	60	1
3	120	1
X	Until ≥ Grade 2 toxicity	

* In the unlikely event of a DLT at this low dose, up to 5 more patients would be accrued at this dose. If >1 DLT was experienced at this dose, a LOWER dose of 15 mg/m^2 would be explored in a further cohort.

Once ≥Grade 2 toxicity is encountered, the standard dose escalation scheme ("3 + 3") will apply and dose escalations will proceed in 25 to 50% increments, although these increments may be modified by discussion with the SRC, according to toxicity or other data accrued in preceding cohorts. If, for example, the first ≥Grade 2 toxicity occurs at the 240 mg/m^2 dose level, the doses shown in Table 4 may be administered. These doses are EXAMPLES and not absolutes until all data from patients in preceding cohorts have been discussed with the Principal Investigators and the SRC. Dose increments generally will be smaller as the MTD is thought to be approaching.

Table 4. Example Doses for Standard Dose Escalation Cohorts

Cohort	Daily Dose (mg/m^2)	Dose Increase	Number of Patients
4	240		3 - 6
5	350	46%	3 - 6
6	475	36%	3 - 6
X	? 600	26%	3 - 6

All SRC discussions and decisions will be documented and patient safety will be the paramount concern.

4.3. Rationale for Study Design

The primary objective of this study is to determine the MTD of CPX-POM in cancer patients with advanced solid tumors. This information will be used to inform the selection of the CPX-POM dose to be used in future studies.

The proposed study design approach is to use a single patient accelerated dose escalation until Grade ≥2 toxicity is observed, followed by a conventional 3+3 design in order to determine the MTD. In view of prior human clinical experience with systemic exposure to CPX, the use of an accelerated, single patient dose escalation scheme in order to minimize patient exposure to suboptimal doses of CPX-POM is warranted.

4.4. Dose Selection

Food and Drug Administration guidelines (FDA, 2010) were employed to determine the starting dose for this study, 30 mg/m^2. As described in this guidance, a common approach for determining a starting dose for small molecule drugs is to use one-tenth the severely toxic dose in 10% of the animals (STD10) in rodents OR one-sixth the highest non-severely toxic dose (HNSTD) in non-rodents. In GLP toxicology studies in rats, the CPX-POM STD10 was not reached, so the highest dose tested (50 mg/kg) was used to determine a safe human starting dose of 30 mg/m^2 (one-tenth the STD10 based on mg/m^2). In GLP toxicology studies in dogs, the CPX-POM HNSTD was 10 mg/kg based on tremors and convulsion observed at 30 mg/kg. One-sixth of the HNSTD observed in dogs, converted to mg/m^2, also supports a starting dose of 30 mg/m^2 in patients.

4.5. End of Study Definition

A patient is considered to have completed the study if he/she has completed the first cycle of the study.

The end of the study is defined as the date of the last procedure for the last patient in the study. At the end of the study the patient will complete the D22 visit as well as the Follow-Up Visit.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1. Patient has histologically- or cytologically- confirmed metastatic or advanced-stage solid malignant tumor that is refractory to standard therapy. Patients should only be included if no therapy exists or if they have received all standard therapies that would be potentially curative or might provide significant benefit.

2. Patient may have received up to 4 prior lines of cytotoxic chemotherapy or immunotherapy for their metastatic disease (e.g., docetaxel + doxorubicin ± cyclophosphamide), and also may have received additional prior endocrine therapy, as appropriate (e.g., for breast or prostate cancer), or non-myelosuppressive therapy (e.g., bevacizumab, trastuzumab).

3. Patient has experienced progressive disease during or following or was intolerant of their most recent treatment regimen. Supporting information about prior progressive disease will be collected, if available.

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

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

6. Patient has an Eastern Cooperative Oncology Group (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 × ULN) or a GFR of ≥50 mL/min).

9. Patient has adequate hepatic function, as evidenced by a total bilirubin ≤1.5 × ULN, AST, and /or ALT ≤3 × ULN or ≤5 ×ULN, if due to liver involvement by tumor.

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 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 (QTc) <470 msec by Fridericia (QTcF). 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.

For the expansion cohort(s) of the study ONLY, if needed:

14. Patient has a specific tumor-type and histology (e.g., locally advanced or metastatic bladder cancer), as designated by the Sponsor based on nonclinical and clinical data obtained prior to enrollment in the Expansion Cohort.

15. Patient has measurable disease, as determined by the Investigator using the Response Evaluation Criteria for Solid Tumors (RECIST), version 1.1 (see Appendix 1).

5.2. Exclusion Criteria

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

1. Patient has a history of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome) or requires the use of concomitant medications that prolong the QT/QTc interval during study participation.

2. Patient has an abnormal cardiac appearance/heart size, as evidenced by chest X-ray or computed tomography (CT) scan.

3. Patient has an uncontrolled or severe intercurrent medical condition (including uncontrolled brain metastases). Patients with stable brain metastases either treated or being treated with a stable dose of steroids/anticonvulsants, with no dose change within 4 weeks before the first dose of CPX-POM and no anticipated dose change, are allowed. 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.

4. Patient underwent major surgery within 4 weeks before the first dose of CPX-POM or received cancer-directed therapy (chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, etc.) or an investigational drug or device within 4 weeks (6 weeks for mitomycin C and nitrosoureas) 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. In addition, any drug-related toxicity, with the exception of alopecia, should have recovered to ≤Grade 1.

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

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

7. Patient has active Hepatitis A infection.

8. Patient 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.

9. 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.

10. Patient is taking warfarin.

11. Patient has a history of other malignancy treated with curative intent within the previous 5 years with the exception of adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix. Patients with previous invasive cancers are eligible if the treatment was completed more than 5 years prior to initiating current study treatment, and there is no evidence of recurrent disease.

12. Patient has known allergy or hypersensitivity to components of CPX-POM.

13. Patient is taking any iron replacement therapy administered IV, IM, or orally due to the potential for loss of anticancer activity due to ciclopirox (the active metabolite of CPX-POM) chelating iron.

5.3. Meals and Dietary Considerations

On Days 1 and 5 of Cycle 1, patients will be required to stay at the clinical research unit for at least 12 hours for PK sampling and other assessments. Patients will be encouraged to drink eight 8-oz glasses of water over a 24-hour period, i.e., 64 oz. total.

If Day 5 Cycle 1 steady state PK assessments are postponed to Day 5 of Cycle 2, the considerations described above will also be postponed to Day 5 of Cycle 2.

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

CPX-POM prodrug, 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

CPX-POM will be administered as an IV infusion once daily on Days 1-5 of each 21-day treatment cycle. CPX-POM will be added to a 100 mL piggyback bag of 0.9% sodium chloride solution and infused over a 10-minute period. The initial dose for the first patient enrolled (i.e., Cohort 1) will be 30 mg/m^2.

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. Thereafter, BSA is to be recalculated on Day 1 of every other treatment cycle, starting with Cycle 3, and the patient's study drug dose adjusted accordingly.

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

The dose escalation procedure is described in Section 4, and further details and example doses are shown in Section 4.2.

After completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated (e.g., adding an additional 5 days of dosing to each treatment cycle).

6.1.5. Dose Modifications

If a patient develops a DLT, CPX-POM dosing should be discontinued until the toxicity is resolved (see definition of a DLT in Section 4). If the toxicity resolves to at least Grade 1, treatment may be re-initiated and the dose of CPX-POM should be reduced by one dose level. If a patient has a second episode of the same DLT despite dose reduction, they should be permanently discontinued from study.

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 (except stable doses being taken for brain metastases), 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. Radiation therapy is also prohibited.

All concomitant medications will be recorded from the time of Screening through the Follow-up Period.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Treatment should be discontinued for a DLT until the toxicity is resolved. If treatment is reinitiated, then the dose of CPX-POM should be reduced as described in Section 6.1.5. If a patient has a second episode of the same DLT despite dose reduction, he or she should be removed from study as outlined in Table 1. Schedule of Assessments (complete D22 and the Early Termination Visit).

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.

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. Cancer Evaluation

All patients will undergo a cancer evaluation to include determination of staging and metastases for screening purposes. Disease response assessments will be performed for patients with measurable disease within 28 days prior to the first dose of CPX-POM and repeated before the first study drug dose (Day 1) of every second cycle (i.e., at approximately 6-week intervals). If a patient with measurable disease discontinues from the study after 6 weeks and before a disease response assessment is scheduled, an additional assessment may be performed, upon consultation with the Sponsor, at the end of treatment (i.e., on approximately Day 22 of the last cycle).

For the screening assessments, all sites of disease will be imaged by CT, if possible. If the anatomic region cannot be adequately imaged by CT, magnetic resonance imaging (MRI) may be used instead. Subsequent assessments should use the same radiographic methods as used during Screening. Disease response will be assessed by the investigator using RECIST, version 1.1 (Eisenhauer et al, 2009; see Appendix 1). Tumor markers applicable to the patient's solid tumor type (e.g., prostate-specific antigen [PSA] for prostate cancer; cancer antigen-125 [CA-125] in ovarian cancer; carcinoembryonic antigen [CEA] in colorectal or pancreatic cancer, cancer antigen 19-9 [CA-19-9] in pancreatic cancer) will also be measured within ±2 days of tumor measurements.

8.2. Safety Assessments

8.2.1. Adverse Events and Serious Adverse Events

8.2.1.1. 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 8.2.2for 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 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 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).

A **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.

8.2.1.2. 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.

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.

8.2.1.3. 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.

8.2.1.4. 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.

8.2.1.5. 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.

8.2.1.6. 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.

8.2.1.7. 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.

8.2.1.8. 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.

8.2.2. 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 8.2.1.4 and 8.2.1.5.

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.

8.2.2.1. 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.

8.2.2.2. 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.

8.2.3. Other Safety and Screening Assessments

8.2.3.1. 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 CT scan to confirm normal cardiac appearance/heart size at Screening.

8.2.3.2. Eastern Cooperative Oncology Group

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 5.

Table 5. Eastern Cooperative 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.

8.2.3.3. 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 Schedule of Assessments, [Table 1]). Body weight should be measured at each study visit. Height should be measured at Screening.

8.2.3.4. 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 Schedule of Assessments (Table 1).

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

8.2.3.5. Electrocardiograms and Holter Monitoring

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 Schedule of Assessments (Table 1).

On Day 1 of Cycle 1, digital Holter monitoring will be performed from 45 minutes pre-dose through 24 hours post-dose in order to examine any potential QTc changes and relate those, if present, to simultaneously obtained blood samples for plasma drug and/or metabolite concentration determination. ECG extractions of the continuous Holter recordings will be performed at 45, 30, and 15 minutes pre-dose and at specific post-dose time points coinciding with the serial blood sampling time points for PK. Patients will be instructed to assume a supine position 5 to 10 minutes prior to each serial blood sampling time point and remain supine throughout the 5-minute ECG extraction period just prior to serial blood sample collection. During the 24-hour Holter monitoring period, a 12-lead ECG tracing may be printed out at any time while the patient is in the clinic at the discretion of the investigator.

If for any reason Holter monitoring is not performed in conjunction with the PK sampling on Day 1 or the tracings are of poor quality, Holter monitoring may be performed in conjunction with the PK sampling on Day 5.

8.2.3.6. Clinical Laboratory Assessments

All protocol-required laboratory assessments, including hematology (including complete blood count), clinical chemistry (including comprehensive metabolic panel), thyroid panel, coagulation testing, and urinalysis must be conducted in accordance with the Study Procedures Manual and the Schedule 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 6.

Table 6. 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 • ALP	• ALT • AST • GGT • Alkaline phosphatase • Direct bilirubin • Indirect bilirubin • Total bilirubin	• Total protein • Albumin • Calcium • Bicarbonate • Magnesium • Phosphate • Lipase • Amylase
Coagulation	• PT	• aPTT	
Thyroid Panel	• TSH	• Free T4	• Free and total T3
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)	• HIV (Screening only)	• Hepatitis A (Screening only) • Hepatitis B (Screening only) • Hepatitis C (Screening only)

Abbreviations: ALP = alkaline phosphatase; 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; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WBC = white blood cell.

8.2.3.7. Ophthalmologic Examinations

Ophthalmologic examinations will be performed by a qualified ophthalmologist at Screening and Follow-up as indicated in the Schedule of Assessments (Table 1). Evaluations will include visual acuity, pupil exam, confrontation visual field, extraocular motility and alignment, interior slit lamp examination, and dilated fundus examination of the retina. Additional ophthalmology evaluations may be requested at any other time, if indicated, as determined by the investigator.

8.3. Pharmacokinetic Assessments

Serial, 3-mL blood (plasma) samples will be taken for PK analysis of CPX-POM and metabolites at the times and days shown in the Schedule of Assessments (Table 1). Each PK sample should be collected as close as possible to the planned time. The actual date and time of each blood sample collection will be recorded. PK samples may not be obtained from the same site where CPX-POM is infused.

Urine samples for PK analysis of CPX-POM and metabolites and measurement of urine volume will be obtained from each patient in urine collection and storage containers. Samples will be collected during Cycle 1 only at the times and days shown in the Study Procedures Manual and the Schedule of Assessments (Table 1). Urine β-glucuronidase activity will be determined in the urine samples collected for PK analysis.

The actual date and time of each 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.

8.4. Pharmacodynamic Assessments

Serial 7-mL blood samples will be collected to characterize the pharmacologic effects of CPX-POM on circulating biomarkers of Wnt and Notch cell signaling pathways at the times and days shown in the Schedule of Assessments (Table 1). Plasma and peripheral blood mononuclear cells (PBMCs) will be isolated from blood. VEGF, IL-6, and IL-8 concentrations will be measured in plasma by enzyme-linked immunoassay (ELISA). Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) will be used to characterize gene expression of circulation biomarkers of Wnt and Notch signaling pathways in PBMCs.

The actual date and time of each 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.

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 maximum anticipated number of patients in the Single Patient and Standard Dose Escalation Cohorts will be approximately 24. In addition to these estimated 24 patients, Expansion Cohort(s) may also be enrolled after the MTD is reached.

The actual number of patients enrolled will depend on the number of dose escalations and the need to further characterize individual cohorts.

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 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, Q1, Q3, minimum, maximum) for each dose group and overall.

9.5.1. Determination of Maximum Tolerated Dose

The MTD is defined as the highest dose at which 1 or fewer of up to 6 patients experience a DLT. The MTD will be exceeded if 2 or more patients in a cohort of up to 6 patients experience a DLT. The number and proportion of patients who experience a DLT or Grade 2 or higher AE will be listed and summarized by dose group. A logistic regression will be used to estimate the predicted toxicity probability at each dose level. Details will be provided in the statistical analysis plan.

9.5.2. Extent of Exposure

Patients' extent of plasma and urine exposure to CPX-POM and metabolites will be summarized by dose group.

9.5.3. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (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 and overall:

9.5.4. 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 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.

9.5.5. Other Safety Evaluations

Physical examination, ECG (including Holter Monitor), ophthalmologic examination, 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

9.6.1. Pharmacokinetics in Plasma

Plasma concentrations of CPX-POM and its metabolites will be determined by GLP-validated liquid chromatography tandem mass spectroscopy(LC-MS/MS) assays. Analysis of resultant plasma CPX-POM (and its metabolites) concentration-time data will be performed using non-parametric PK data analysis methods using Phoenix WinNonlin 7.0 (Certara LP, Princeton, NJ). PK parameters will be listed and summarized for each analyte using descriptive statistics (e.g., sample size, arithmetic mean, % coefficient of variation, standard deviation, median, minimum, and maximum). The following PK parameters will be determined:

- C_{max} - Maximum observed plasma concentration (C_{max}) observed following administration of a single dose on Day 1
- T_{max} - Time to reach maximum observed plasma concentration (C_{max})
- $AUC_{[0\text{-}t]}$ - Area under the concentration-time curve following administration of a single dose on Day 1
- $AUC_{[t\text{-}\infty]}$ - Area under the concentration-time curve following administration of a single dose on Day 1 from the last quantifiable concentration (t) to infinity.
- AUC_{inf} - Area under the curve from time zero to extrapolated infinite time [$AUC_{(0\text{-}\infty)}$] following administration of a single dose on Day 1 as the sum of $AUC_{[0\text{-}t]} + AUC_{(t\text{-}\infty)}$
- Css_{max}- Maximum observed plasma concentration at steady-state on Day 5
- Tss_{max} - Time to reach maximum observed plasma concentration (Css_{max}) on Day 5
- AUC_{SS} - Area under the concentration-time curve over the dosing interval at steady-state following drug administration on Day 5
- λ - Apparent first-order elimination rate constant
- t½ - Apparent elimination half-life
- Cls – Systemic clearance following administration of a single dose on Day 1
- Clss – Systemic clearance at steady-state
- Vd – Apparent volume of distribution
- Vss – Steady-state volume of distribution

- C_{max} Derived Accumulation Ratio - Css_{max}/C_{max}
- AUC Derived Accumulation Ratio - $AUCss/AUC_{(0-\infty)}$
- CL_r – Single dose (Day 1) and steady-state (Day 5) renal clearance

Plasma drug and metabolite concentration-time data and derived plasma PK parameters will be presented in tabular and graphic format.

9.6.2. Pharmacokinetics in Urine

Urine concentrations of CPX-POM and its metabolites will be determined by GLP-validated LC-MS/MS assays. Urine PK parameters will be generated using non-parametric PK data analysis methods, listed, and summarized for each analyte using descriptive statistics (e.g., sample size, arithmetic mean, % coefficient of variation, standard deviation, median, minimum, and maximum). The following PK parameters will be determined:

- Mass excreted
- Excretion rate
- Cumulative mass excreted

Urine β–glucuronidase activity will be measured for each patient and summarized.

9.6.3. Covariates and Pharmacokinetics

The influence of dose, single versus multiple dose administration, β-glucuronidase activity, and other potential covariates (e.g., creatinine clearance, concomitant medications, concurrent disease) on CPX-POM and metabolite exposure will be examined in an exploratory fashion given the limited sample size.

9.7. Pharmacodynamic Analyses

The pharmacologic effects of CPX-POM on circulating Wnt and Notch cell signaling biomarkers will be characterized. Plasma concentrations of VEGF, IL-6, and IL-8 will be determined prior to, during, and following CPX-POM treatment for each cycle by ELISA. Expression of survivin; Notch receptors 1, 2, and 3; Notch ligand Jagged-1, Notch target proteins HES1, Hey1, cyclin D1, and cMyc; as well as ϒ-Secretase proteins Presinilin-1 and Nicastrin, will be determined in PBMCs by qRT-PCR.

Relationships between observed biomarker changes and drug and/or metabolite exposure as well as other measures will be explored using descriptive statistics, and/or additional PK/PD modeling to support the dose selection for future studies. Demographic and baseline characteristics may be included in the modeling analysis.

9.8. Interim Analyses

No formal interim analysis is planned. After each cohort is completed, an SRC comprised of the CRO Medical Monitor, Principal Investigator(s), and Sponsor representatives will meet to discuss the data and decide upon the next dose escalation. In addition, after completion of Cycle 1 for the first 4 to 6 patients, the SRC will review safety, PK, and PD data to determine if any changes to the dosing schedule are indicated.

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/IEC 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.

11. REFERENCES

Abrams BB, Hanel H. Hoehler T. Ciclopirox olamine: a hydroxypyridone antifungal agent. *Clin Dermatol*. 1991;9(4):471-477.

Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomyosis. *J Am Acad Dermatol*. 2000;43(4):S57-S69.

Clement PMJ, Hanauske-Abel HM, Wolff EC, Kleinman HK, Park MH. The antifungal drug ciclopirox inhibits deoxyhpusine and proline hydroxylation, endothelial cell growth and angiogenesis in vitro. *Int J Cancer*. 2002;100:491-498.

ClinicalTrials.gov web site. Available at: https://clinicaltrials.gov/. Accessed May 18, 2017.

CPX-POM Investigator's Brochure. CicloMed LLC. 2017.

Dihazi H, Dihazi GH, Jahn O, Meyer S, Nolte J, Asif AR, Mueller GA, Engel W. Multipotent adult germline stem cells and embryonic stem cells functional proteomics revealed an important role of eukaryotic initiation factor 5A (Eif5a) in stem cell differentiation. *J Proteome Res*. 2011;10:1962-1973.

Eberhard Y, McDermott SP, Wang X, Gronda M, Venugopal A, Wood TE, Hurren R, Datti A, Batey RA, Wrana J, Antholine WE, Dick JE, Schimmer AD. Chelation of intracellular iron with the antifungal agent ciclopirox olamine induces cell death in leukemia and myeloma cells. *Blood*. 2009;114(14):3064-3073.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shakar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

[FDA] Food and Drug Administration. Guidance for Industry – S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. March 2010. Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm085389.pdf. Accessed September 18, 2017.

Gupta AK. Ciclopirox: an overview. *Int J Dermatol.* 2001;40(5):305-310.

Gupta AK, Plott T. Ciclopirox: a broad-spectrum antifungal with antibacterial and anti-inflammatory properties. *Int J Dermatol*. 2004; 43(Suppl 1):3-8.

Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part 1. *J Am Acad Dermatol*. 1994;30(5 Pt 1):677-698.

Hanel H, Smith-Kurtz E, Pastowsky S. Therapy of seborrheic eczema with an antifungal agent with an antiphlogistic effect. *Mycoses*. 1991;34(Suppl 1):91-93.

Kellner HM, Arnold C, Christ OE, Eckert HG, Herok J, Hornke I, Rupp W. Investigations on the pharmacokinetics and biotransformation of the antimycotic ciclopiroxolamine in animals and humans after topical and systemic application. *Anzneim-Forsch/Drug Res.* 1981; 31(II). No. 8a:1337-1353.

Kwong W-L, Lok C-N, Tse C-W, Wong E L-M, Che C-M. Anti-cancer iron(ii) complexes of pentadentate n-donor ligands: cytotoxicity, transcriptomics analyses, and mechanisms of action. *Chem Eur J.* 2015;21:3062–3072.

Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase 1 cancer clinical trials. *JNCI*. 2009;101(10):708-720.

Minden MD, Hogge DE, Weir SJ, Kasper J, Webster DA, Patton L, Jitkova Y, Hurren R, Gronda M, Goard CA, Rajewski LG, Haslam JL, Heppert KE, Schorno K, Chang H, Brandwein JM, Gupta V, Schuh AC, Trudel S, Yee KW, Reed GA, Schimmer AD. Oral ciclopirox olamine displays biological activity in a phase 1 study in patients with advanced hematologic malignancies. *Am J Hematol*. 2014; 89(4):363-368.

Oken M, Creech R, Tormey D, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Sakurai K, Sakeguchi T, Yamaguchi H, Iwata K. Mode of action of 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone ethanolamine salt (Hoe296). *Chemotherapy*.1978;24(2):68-76.

Sidarovich V, Adami V, Gatto P, Greco V, Tebaldi T, Tonini GP, Quattrone A. Translational downregulation of hsp90 expression by iron chelators in neuroblastoma cells. *Mol Pharmacol.* 2015;87(3):513-524.

Song S, Christova T, Perusini S, Alizadeh S, Bao RY, Miller BW, Hurren R, Jitkova Y, Gronda M, Isaac M, Joseph B, Subramanian R, Aman A, Chan A, Hogge DE, Weir SJ, Kaspar J, Schimmer AD, Al-awar R, Wrana JL, Altisano L. WNT inhibitor screen reveals iron dependence of β-catenin signaling in cancers. *Cancer Res*. 2011;71:7628-7639.

Szüts D, Krude T. Cell cycle arrest at the initiation step of human chromosomal DNA replication causes DNA damage. *J Cell Sci.* 2004;117(Pt 21):4897-4908.

12. APPENDIX

Appendix 1. RECIST Criteria Guidance

Time Point Response of Measurable Disease (Target Lesions) with or without Non-Measurable Disease (Non-Target Lesions)

Target Lesion Response	Non-Target Lesion Response	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = Not All Evaluated

Time Point Response of Non-Measurable Disease Only (Non-Target Lesions)

Non-Target Lesion Response	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Con-PD
NE	No	NE
Unequivocal Progression	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = Complete Response, PD = Progressive Disease, NE = Not All Evaluated
Note: Non-CR/Non-PD is preferred over "Stable Disease" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials, so to assign this category when no lesions can be measured is not advised

Note: If a CR is truly met at a time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that time point since disease must have reappeared after CR.

Source: Eisenhauer et al, 2009