A phase 2 basket trial of ulixertinib (BVD-523) in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring MAPK pathway mutations (BVD-523-HCQ)

Investigational Product	Ulixertinib (BVD-523)
Phase	2
Sponsor	BioMed Valley Discoveries, Inc. Address: BioMed Valley Discoveries, Inc. 4435 Main Street, Suite 550 Kansas City, MO 64111
IND	IND 115451
NCT number	NCT05221320
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DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol v. 1.0	19 October 2021	Not applicable
Amended protocol v. 2.0	02 May 2023	Updated definition of evaluable patients
Amended Protocol v.3.0	28 August 2023	Updated header Updated inclusion criteria language Updated Appendix 3 (Conmeds)

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: BIOMED VALLEY DISCOVERIES, INC

I have read and understand the contents of version 2.0 of this clinical protocol for Study No. BVD-523-HCQ dated 02 May 2023 and I agree to meet all obligations of the sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Approved By:

Brent L. Kreider, PhD.	Date
President, BioMed Valley Discoveries, Inc.	

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of version 2.0 of this clinical protocol for Study No. BVD-523-HCQ dated 02 May 2023 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current Good Clinical Practices and applicable FDA regulatory requirements:

Principal Investigator:

Name:

Title:

Institution:

Address:

Address:

Phone:

Fax:

Signature	**Date**

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1 STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial patients. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent, using a previously approved consent form.

2 ABBREVIATION AND DEFINITION OF TERMS

Abbreviation	Definition/Explanation
ACI	As clinically indicated
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCVA	Best-corrected distance visual acuity
β-hCG	Beta-human chorionic gonadotropin
BID	Twice daily
BP	Blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CA	Cancer antigen
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case report form
CRO	Clinical research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
CQ	Chloroquine
DCF	Docetaxel, Cisplatin, and 5-fluorouracil
DILI	Drug-Induced Liver Injury
EAS	Efficacy analysis set
ECF	Epirubicin, cisplatin and 5-fluorouracil
EDC	Electronic data capture

Abbreviation	Definition/Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
EOT	End of Treatment
ERK	Extracellular signal-regulated kinase
FAS	Full Analysis Set
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCQ	Hydroxychloroquine
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
HRAS	Harvey rat sarcoma virus
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IUD	Intra-uterine device
IUS	Intra-uterine hormone-releasing system
KRAS	Kirsten rat sarcoma virus
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MEK	MAPK kinase
MMR	Measle Mumps Rubella
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NRAS	Neuroblastoma RAS
ORR	Overall response rate
PD	Pharmacodynamic(s)
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response

Abbreviation	Definition/Explanation
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma
RECIST	Response evaluation criteria in solid tumors
RPPA	Reverse-phase protein array
SAE	Serious adverse event
SOA	Schedule of Activities
SD	Stable disease
SD-OCT	Spectral-domain ocular coherence tomography
$t_{1/2}$	Terminal elimination half-life
TB	Tuberculosis
TdP	Torsades de Pointes
t_{max}	Time of maximum observed concentration
ULN	The upper limit of normal
VF	Visual field
V600E	A mutation of the BRAF gene in which valine (V) is substituted by glutamic acid (E) at amino acid 600

3 PROTOCOL SUMMARY

3.1 Synopsis

Title: A phase 2 basket trial of ulixertinib (BVD-523) in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring MAPK pathway mutations (BVD-523-HCQ)

Study Description: This is an open-label, prospective phase 2 basket trial assessing the efficacy of ulixertinib in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies. All patients enrolled must have a MAPK activating mutation to be deemed eligible for trial participation. Each disease-based basket will open to enrollment in two stages. The opening of stage two will be dependent on the observed responses in the patients enrolled in the first stage.

Objectives:

Primary Objectives:

- To assess the safety and tolerability of ulixertinib and hydroxychloroquine in patients with advanced, RAS, non-V600 BRAF, MEK1/2, or ERK1/2 mutated gastrointestinal (GI) malignancies.
- To assess the efficacy of ulixertinib and hydroxychloroquine in patients with advanced, RAS, non-V600 BRAF, ERK1/2, or MEK1/2 mutated gastrointestinal malignancies.

Secondary Objective:

- To assess the duration of efficacy of ulixertinib and hydroxychloroquine in patients with advanced RAS, non-V600 BRAF, MEK1/2, or ERK1/2 mutated gastrointestinal malignancies.

Exploratory Objective:

- To evaluate the bioactivity of ulixertinib and hydroxychloroquine against ERK1/2, autophagy pathways, and pharmacodynamic biomarkers.

Endpoints:

Primary Endpoints:

- The incidence and frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.
- Overall response rate as defined by the proportion of patients achieving a confirmed PR and CR (defined by RECIST 1.1) as evaluated by the local treating investigator.

Secondary Endpoint:

- Progression-free survival (PFS) as defined as the time from study drug initiation to the time of documented disease progression (as assessed by RECIST 1.1) or death from any cause.

Exploratory Endpoint:

- Pharmacokinetics (PK) of ulixertinib and hydroxychloroquine.
- Blood and/or tissue samples used to assess biomarkers (RPPA, Nanostring, circulating tumor (ctDNA) examples of assays planned but not limited to only these).

Study Population:

Key Inclusion Criteria:

- Patient with histologically confirmed advanced gastrointestinal malignancy harboring a MAPK-mutated GI malignancy: KRAS, NRAS, HRAS, BRAF non-V600, MEK1/2 (MAP2K1/2), and ERK1/2 (MAPK3/1).
- Patients must have been previously treated with one or more lines of anti-cancer therapy and have documented disease progression during or after their most recent line of anti-cancer treatment subject to the restrictions below (variations of standard of care may exist and are acceptable). Patients with cholangiocarcinoma, esophageal, GEJ cancer and gastric cancer who are stable on second-line regimens or beyond are eligible for trial participation if current treatment becomes intolerable.
- Measurable disease per RECIST 1.1 criteria.

- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1.

Key Exclusion Criteria:

- Prior therapy washout:
  - Systemic antineoplastic therapy including investigational: ≤ 14 days or within five half-lives prior to starting study treatment, whichever is shorter.
  - Radiotherapy ≤ 14 days prior to the first dose of study treatment.
- Known uncontrolled brain metastases or cranial epidural disease.

Phase:	2
Description of Study Intervention:	Ulixertinib 450 mg orally twice daily Hydroxychloroquine 600 mg orally twice daily.
Study Duration:	Approximately 35 months from when study opens to enrollment until completion of data analyses
Patient Duration:	Each patient will continue on study treatment until documented disease progression, intolerable toxicity, study closure, or until other treatment discontinuation criteria is met. Patients who discontinue study treatment prior to disease progression, will continue to be followed for progression. It is estimated that patients will be on study for up to two years.

3.2 Schema

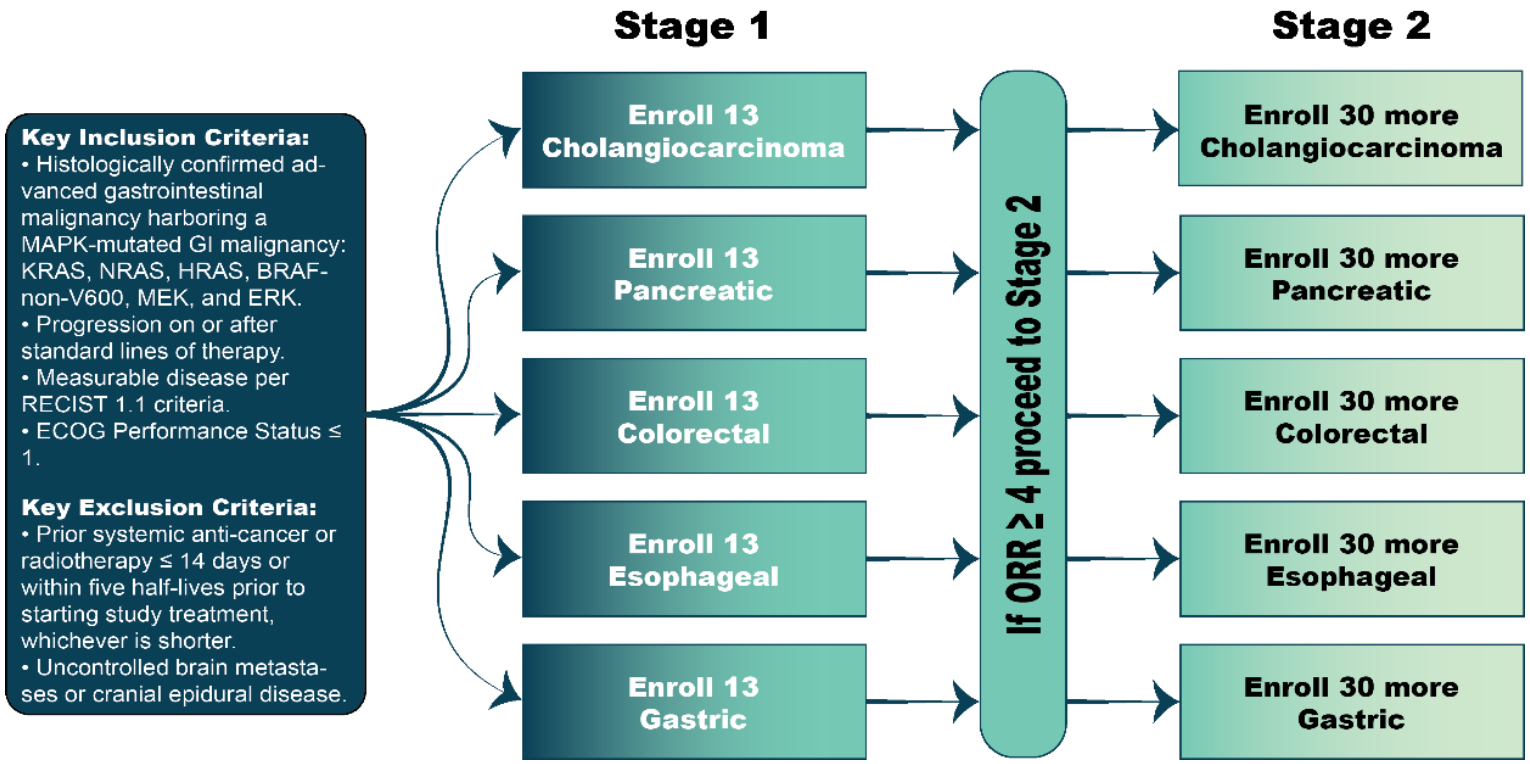

Figure 1: Study Schema

Abbreviations: ECOG = Eastern Cooperative Oncology Group; GI = Gastrointestinal; ORR= Overall Response Rate; RECIST = response evaluation criteria in solid tumors. Note: The numbers given under stage 1 and 2 represent the numbers of patients in each cohort.

3.3 Schedule of Activities

The Schedule of Activities table (Table 1) provides an overview of the protocol visits and procedures. Refer to Section 9 and Section 10 for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities (SOA) table to conduct evaluations or assessments required to protect the well-being of the patient. Every effort should be made to follow the SOA for the entire study.

Table 1: Schedule of Assessments and Procedures

Protocol Activities	Screening[1]	On-Treatment Period: One Cycle = 28 days						Post-Treatment Period		
		Cycle 1			Cycle 2		Cycle 3+	EOT[2]	Safety Follow-Up[3]	Follow-Up
Day of Cycle (Visit Window)	(≤ -28 days)	1[4]	8 (± 2 days)	15 (± 2 days)	1 (± 2 days)	15 (± 2 days)	1 (± 2 days)	**(+7 days)**	**(± 7 days)**	
Informed Consent	X									
Demographics	X									
Cancer History[5]	X									
Medical History	X									
Eligibility Criteria	X									
Clinical Assessments										
Vital Signs[6]	X	X	X	X	X	X	X	X	X	
Physical Exam[7]	X	X	X	X	X	X	X	X	X	
ECOG Score	X	X	X	X	X	X	X	X	X	
ECG	X		X	X	X			X		
Echocardiogram	X	ACI								
Ophthalmologic Exam[8]	X				X		X			
Adverse event collection	X	X								
Concomitant medications	X	X								
Laboratory Studies[9]										
Hematology	X	X	X	X	X	X	X	X	X	

Protocol Activities	Screening[1]	On-Treatment Period: One Cycle = 28 days						Post-Treatment Period		
		Cycle 1			Cycle 2		Cycle 3+	EOT[2]	Safety Follow-Up[3]	Follow-Up
Day of Cycle (Visit Window)	(≤ -28 days)	1[4]	8 (± 2 days)	15 (± 2 days)	1 (± 2 days)	15 (± 2 days)	1 (± 2 days)	(+7 days)	(± 7 days)	
Chemistry	X	X	X	X	X	X	X	X	X	
Creatine kinase[10]	X	ACI								
LDH and Phosphorus	X	X	X	X	X	ACI				
Coagulation	X	ACI								
Urinalysis	X	ACI								
Tumor Marker[11]		X			X		X	X		
Pregnancy Test[12]	X	ACI								
Disease Assessments										
CT Scans or MRI[13]	X						X	X		X[14]
RECIST 1.1 Assessment	X						X	X		X
Treatment Compliance and Distribution										
Hydroxychloroquine		X			X		X			
Ulixertinib		X			X		X			
Treatment administration on site				X[15]			X			
Meal provided by site				X			X[16]			

Abbreviations: ACI = as clinically indicated; LDH = lactate dehydrogenase; CT = computed tomography; MRI = magnetic resonance imaging; ECG = electrocardiogram; EOT = end of treatment

[1] Screening procedures must be completed ≤ 28 days prior to C1D1 unless noted otherwise.
[2] The end of treatment visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. All end of treatment procedures should be completed within 7 days after the decision to discontinue treatment has been made.
[3] Patients will have a safety follow-up visit 60 days (± 7 days) after last dose of study drug.
[4] C1D1 procedures do not need to be repeated if screening procedures were performed ≤ 7 days of the start of treatment.

[5] Oncologic history of the malignancy under study including prior regimens (duration of therapy, best response on therapy, date of discontinuation, and reason for discontinuation), surgery, and radiation therapy.
[6] Vital signs include systolic/diastolic blood pressure, heart rate, respiration rate, pulse oximetry, weight, and body temperature. Height will be captured at screening only.
[7] If necessary to facilitate scheduling, the physical exam may occur one day prior to study treatment.
[8] A standard ophthalmologic exam must be completed at screening, C2D1, and every 3 cycles thereafter (i.e. C5D1, C8D1, etc.) and as clinically indicated to assess for retinopathies. All assessments must be conducted up to 7 days prior to the clinic visit to enable timely results review.
[9] Labs may be performed ≤ 3 days prior to a scheduled day one visit except for C1D1 labs which may be completed ≤ 7 days prior to C1D1.
[10] After screening, creatine kinase should only be drawn if creatinine is elevated.
[11] Tumor marker should be drawn on day one of each cycle. Tumor markers will be disease specific: pancreatic adenocarcinoma only CA 19-9; colorectal carcinoma only CEA; cholangiocarcinoma only CEA and CA 19-9. Tumor markers are not required for patients with esophageal or stomach cancers.
[12] Pregnancy test (serum or urine) must be obtained at screening ≤ 7 days prior to C1D1 for all women of childbearing potential and as clinically indicated while on treatment.
[13] Disease assessment will be repeated every 8 weeks (± 7 days) regardless of dose holds or delays. Patients who discontinue treatment for reasons other than progression will have computed tomography (CT) scans at the EOT visit (unless their previous restaging was performed within 6 weeks).
[14] Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression or initiation of subsequent anticancer therapy.
[15] Patient should be instructed to not take their study treatment before arriving at clinic. Study treatment and meal should be provided after the pre-dose PK draw.
[16] Meal is only required to be given at C3D1, i.e., at the time of drug administration for ctDNA and tumor biopsy for stage 1.

Table 2: Schedule of Correlative Sample Collection

Correlative Test	Screening	C1D1	C1D15								C3D1	EOT
			Pre-Dose	Post-Dose								
Time Point (hour)				0.5	1	2	4	6	8	12	± 7 days	
Window (min)			≤ 60	±2	±3	±6	±12	±18	±24	±36		
STAGE 1												
PK Blood[1]			X	X	X	X	X	X	X	X		
ctDNA		X									X[2]	X[3]
Biopsy[4]	X										X	X
STAGE 2												
PK Blood			X									

Abbreviations: C = cycle; ctDNA = circulating tumor DNA; D = day; EOT = end of treatment; PK = pharmacokinetics.

[1] To accommodate PK blood draws, patients should be instructed not to take their morning doses of both medications until told to do so in the clinic. A meal should be provided by the site when taking the medications in the clinic. Pre-dose PK sample should be collected prior to the administration of study drugs. Post-dose PK samples should be collected at the appropriate time points following administration of study drugs. PK samples should be drawn while patients are at steady state, which is 5 days, or 10 consecutive doses.
[2] To be drawn at the time of the tumor biopsy.
[3] Required blood draw at EOT. If optional biopsy is collected at EOT, ctDNA should be drawn at the time of the tumor biopsy.
[4] Biopsies at screening and C3D1 (± 7 days) are required. When blood is being drawn at D3D1, site will provide a meal when study drugs are taken. An optional biopsy will be offered at the time when the decision to discontinue treatment is made (+ 7 days).

4 INTRODUCTION

4.1 Study Rationale

The mitogen-activated protein kinase (MAPK) pathway is a second messenger system that plays a key role in the regulation of the cell cycle. However, mutations in key kinases within the pathway leads to a loss of regulation and oncogenesis. Many targeted inhibitors have been developed to stop the persistent downstream signaling created by driver mutations at RAS, RAF, MEK, and ERK[1]. Yet, resistance mechanisms arise that skirt the inhibition imposed by these targeted therapies.[2-4] Increased levels of autophagy, or self-consumption, have been found to correlate with pharmacologic resistance.[5] Pre-clinical data has shown that blockade of MAP kinase pathway leads to upregulation of autophagy.[6] Pre-clinical data has also demonstrated that targeted kinase inhibition in combination with autophagy inhibition has a synergistic antitumor effect.[7] Therefore, we propose to combine hydroxychloroquine, an autophagy inhibitor, with ulixertinib, an ERK inhibitor, in MAPK-mutated gastrointestinal malignancies.

4.2 Gastrointestinal Malignancies

Gastrointestinal malignancies are the second leading cause of death in the United States despite the downward trend of incidence and mortality in recent years. In 2019, an estimated 165,460 deaths and 328,030 new cases will occur. [8] Regardless of recent advances in oncology, the relative 5-year survival rate for patients diagnosed with a gastrointestinal malignancy remains low: esophageal (21%), cholangiocarcinoma (19%), pancreatic (9%), and stomach (32%).

Empowered by Next Generation Sequencing, precision pharmacology has sought to identify and target disease-driver mutations. While targeted therapies have seen much success in other malignancies (such as melanoma and non-small cell lung), gastrointestinal malignancies have demonstrated little efficacy and only a few are approved by the Food and Drug Administration (FDA) for use in this patient population.

4.3 MAPK-Mutated Gastrointestinal Malignancies

The MAPK pathway is a second messenger system transmitting signals from extracellular stimuli, such as growth factors, to the nucleus. The extracellular signal is propagated through a series of downstream phosphorylation events cumulating in the regulation of genes responsible for cell survival and proliferation.[1] However, genetic mutations that alter the function of the protein kinases along the pathway have been linked to oncogenesis and the promotion of cell migration and metastasis in a variety of cancers.[2,3] Common sites for mutations leading to persistent pathway activation are often described in the RAS, RAF, MEK, and ERK protein families.

The RAS proteins, HRAS, NRAS, and KRAS, are GTPases that activate the RAF proteins in the signaling cascade. About one-third of malignancies contain an activating mutation in a RAS protein generating continual downstream signaling in the absence of extracellular stimuli.[10] The

most common of these mutations is KRAS with the highest reported frequency among pancreatic cancer and right-sided colorectal patients. [11] Table 3 lists the frequency of RAS mutations by cancer type.

Table 3: Frequency of RAS mutations by cancer type[11]

	KRAS (%)	NRAS (%)	HRAS (%)
Colorectal cancer	27 – 56	1-7	< 1
Stomach cancer	2.85 – 9.4	1.9	< 1
Pancreatic cancer	90	< 1	< 1
Cholangiocarcinoma	16 – 38	Limited Data	< 1

RAS proteins activate kinases of the RAF family: ARAF, BRAF, and CRAF. BRAF mutations are well documented as drivers of malignancy, primarily in melanoma and non-small cell lung cancers.[6,7] $BRAF^{V600E}$ mutation allele is the most common oncogenic variant and is standardly treated with a targeted inhibitor (vemurafenib or dabrafenib). However, $BRAF^{non\text{-}V600E}$ mutations occur in about 18% of advanced malignancies and have demonstrated lower efficacy to these approved agents.[14]

RAF proteins phosphorylate MEK1 and MEK2 and in turn, MEK proteins activate ERK1 and ERK2. While MEK and ERK mutations are rare, they can propagate the signal leading to oncogenesis.

4.4 MAP Kinase Inhibition

Due to the multiple kinases involved in the MAPK phosphorylation cascade, multiple opportunities for pharmacologic inhibition exist. It was noted that BRAF mutations are common in melanoma and so the race to target BRAF began. The first BRAF inhibitor, sorafenib, was a dirty kinase inhibitor with poor specificity which led to poor tolerance at therapeutic doses.[9-11] These off-target effects motivated the development of a more specific BRAF inhibitor, vemurafenib. Clinical trials quickly demonstrated improved objective response rates, progression-free survival (PFS), and overall survival (OS) which led to FDA approval in 2011.[12] Later, dabrafenib followed after demonstrating similar efficacy.[19]

Similar to BRAF, KRAS mutations were commonly described as drivers of oncogenesis. However, after many attempts to develop an inhibitor, KRAS was deemed “undruggable”[20] and pharmacologic development turned its attention downstream to MEK. As the kinase downstream of RAS and RAF, MEK appeared to be a great opportunity for stopping pathway over-activation originating from RAS, RAF, and MEK mutations. This led to the eventual development and approval of trametinib.[21]

Despite the clinical success of these inhibitors, experience quickly demonstrated that resistance persistently develops 6 – 8 months after the start of BRAF and MEK therapies.[16,17] Combining MEK and BRAF inhibitors seemed to delay the development of secondary resistance and generated approval for multiple BRAF and MEK inhibitor combinations.[16-19] Combined inhibition of the MAPK pathway has demonstrated improved efficacy and delayed the development of resistance in melanoma[20,21] and non-small cell lung cancer.[22,23] Yet even with inhibition at two points in the MAPK pathway, patients that initially demonstrate a response acquire resistance and disease progression soon after starting therapy.

4.4.1 Mechanisms of Resistance

The secondary or acquired mechanisms of resistance that arise from MAPK pathway inhibition are classified into pathway-dependent and pathway independent. Pathway-dependent based resistance arises as an “escape” from pathway inhibition. By this mechanism, BRAF and MEK kinases develop alternative mutations that block the binding pocket used by inhibitors.[16,17,24] Pathway independent resistance is characterized by overexpression of regulating tyrosine kinases to compensate for pathway inhibition or increased cross-talk from the AKT pathway which activates ERK. [3] However, either mechanism of resistance leads to ERK reactivation.

However, a new understanding of the connection between the autophagy and the MAPK pathways is developing. Cytoprotective autophagy is a catabolic pathway that includes the lysosomal degradation of proteins to support cellular metabolism during times of cellular stress. [28] By recycling cellular components, the cancer cell manages to continue to fuel its high metabolic needs despite the potentially cytotoxic effects of pathway inhibition. Not only do MAPK-mutated cells rely on a higher level of baseline autophagy[26], but it has also been demonstrated that cells with higher levels of resistance also have increased levels of autophagy. [27] Kinsey et al. have shown that inhibition of KRAS→RAF→MEK→ERK signaling in pancreatic ductal adenocarcinoma cell lines elicits autophagy, a process of cellular self-consumption. [28]

Ojha et al. have described a process by which ERK reactivation and autophagy arise when MEK or BRAF inhibitors are introduced.[30] They demonstrated that with the introduction of MEK and BRAF inhibitors, the MAPK pathway is translocated into the endoplasmic reticulum (ER). Within the ER, the accumulation of proteins produces ER stress and initiates the Unfolded Protein Response (UPR) in an effort to restore ER proteostasis. [28] UPR initiation causes GRP78 to disassociate from Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK). PERK, in turn, upregulates the transcription of ATF4 and phosphorylates ERK.[25,29] In turn, pERK phosphorylates ATF4 which increases cellular autophagy and cell survival.

Therefore, as the last master kinase in the MAPK pathway and a key to acquired resistance, ERK plays a large role in oncogenesis and is an appealing target for pharmacologic inhibition.

4.4.2 Pre-Clinical Experience

Due to the complex interaction between the autophagy pathway and ERK, the combination of pathway inhibition and an autophagy inhibitor should have complementary effects. Combined

inhibition of MEK1/2 and autophagy with chloroquine (CQ) has displayed synergistic anti-proliferative effects against pancreatic ductal adenocarcinoma (PDAC) cell lines *in vitro*. [28] Most strikingly, whereas single-agent therapy had modest effects, combined treatment of xenografted patient-derived PDAC tumors with trametinib plus chloroquine/ hydroxychloroquine elicited striking tumor regression. In these experiments, the regression elicited by trametinib plus chloroquine/hydroxychloroquine was superior to gemcitabine/ nab-paclitaxel, standard of care chemotherapy. Similar effects have been seen in BRAF inhibitor-resistant melanoma. [27]

Bryant et al. combined ERK (ulixertinib) and autophagy inhibition (chloroquine) in KRAS mutated PDAC cells.[30] They demonstrated that ERK inhibition and suppression of KRAS increased cellular dependence on autophagy for survival. When chloroquine was added as an autophagy inhibitor, synergistic antitumor activity was observed in organoid and PDX models.

4.5 Investigational Intervention

4.5.1 Ulixertinib

Ulixertinib is a highly potent small-molecule inhibitor of extracellular signal-regulated kinase, ERK1 and ERK2. It competitively and reversibly binds to the adenosine triphosphate (ATP) binding site in a dose-dependent manner. It effectively binds with ERK in its phosphorylated and de-phosphorylated state thereby inhibiting phosphorylation of ERK substrates. Ultimately, this inhibition of downstream signaling leads to inhibition of cell proliferation and survival.)

Following administration, ulixertinib plasma concentration reaches maximum observed concentration (C_{max}) in 3 to 4 hours (t_{max}) and remains sustained for about 2 to 4 hours. After reaching C_{max}, plasma concentrations slowly decline with a half-life ($t_{1/2}$) ranging from 4 to 6 hours. Ulixertinib is primarily metabolized by CYP3A4 and to a lesser extent CYP2D6 and CYP1A2 by oxidation and de-alkylation. No significant cytochrome P450 (CYP) induction was observed after up to 14 days of drug treatment in rats. *In vitro,* human liver microsome studies do demonstrate ulixertinib to induce CYP1A2, CYP2B6, and CYP3A4 mRNA expression, whilst also directly inhibiting CYP2C8 and CYP3A4/5. These data suggest limited potential for drug-drug interactions. Fecal excretion is the primary route of elimination around 82% with about 15% excreted renally.

The most commonly reported treatment-related AEs are consistent with other drugs that inhibit the MAPK pathway: fatigue, diarrhea, nausea, dermatitis acneiform, and vomiting. However, phototoxicity, hematologic, hepatic, ophthalmologic, and cardiac effects have been noted in a small proportion of patients. Refer to the most recent Investigator's Brochure (IB) for more information.

4.5.2 Previous Human Experience

Ulixertinib has been administered to humans in 5 commercially sponsored clinical studies, 4 Investigator sponsored trials and 3 NCI sponsored trials to date:

Table 4: Previous Human Experience with Ulixertinib

Study Type	Study Identifiers	Status/Results
Commercial sponsored	NCT01781429 BVD-523-01 Phase 1 Dose-Escalation, Safety, Pharmacokinetic and Pharmacodynamic Study of BVD-523 in Patients with Advanced Malignancies.	In the first in human, phase I study of ulixertinib a total of 135 patients were enrolled in the dose escalation and dose expansion phases of the study. Twenty-seven patients were enrolled in the dose escalation phase (10-900 mg b.i.d.). The maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) was determined to be 600 mg twice daily given continuously. Dose-limiting toxicities (DLT) included rash, diarrhea, elevated AST, and elevated creatinine. Drug exposure was dose proportional up to the RP2D, which provided near-complete inhibition of ERK activity in whole blood. In the expansion cohort (108 patients), there were no drug-related deaths; however, 32% of patients required a dose reduction. The most common adverse events (AEs) at RP2D, regardless of attribution, were diarrhea (50%), fatigue (50%), nausea (45%), decreased appetite (31%), and dermatitis acneiform (31%). In addition to 3 patients with partial responses during escalation (11%), an additional 11 of 81 (14%) evaluable patients at expansion had a partial response: 1 $BRAF^{V600E}$ mutant melanoma patient refractory to prior BRAF/MEK inhibitor treatment, 3 NRAS mutant melanoma patients, 3 patients with BRAF mutant lung cancers including response in brain metastases, 1 with $BRAF^{V600E}$ mutant glioblastoma multiforme, 1 with $BRAF^{G469A}$ head & neck cancer, 1 with $BRAF^{G469A}$ small-bowel cancer, and 1 with $BRAF^{L485W}$ gallbladder cancer. The duration of response ranged from 2 to 24+ months (82, 98). A total of 28 evaluable patients whose BRAF mutations were not at amino acid V600 were included in the BVD-523-01 solid tumor study of ulixertinib.
Commercial sponsored	NCT00296242 BVD-523-02 Phase 1/2 Dose-Escalation, Safety, Clinical Activity, Pharmacokinetic and Pharmacodynamic Study of the ERK 1/2 Inhibitor BVD-523 in Patients with Acute Myelogenous Leukemia or Myelodysplastic Syndromes	An open-label, multicenter Phase I/II study to determine the safety, tolerability, and pharmacokinetic profile of ulixertinib in patients with acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS), as well as to assess clinical response, progression-free survival (PFS), and duration of response in those patients. The study consisted of 2 parts: Part 1 was a dose-escalation phase to investigate safety and determine the MTD and the RP2D, and Part 2 was a cohort-expansion phase using the RP2D to examine safety, and to identify early indications of clinical effects. Patients received continuous twice-daily oral dosing with ulixertinib in 21-day cycles. A total of 18 patients received at least one dose of ulixertinib in the dose-escalation phase (300-750mg b.i.d.). In Part 1, the MTD and RP2D were determined to be 600 mg b.i.d., and this is the dose that was tested in the cohort-expansion phase (Part 2) of the study. A total of 35 patients received at least one dose of ulixertinib in the cohort-expansion phase of the study. Of the 35 patients in Part 2, 14 patients (40%) were RAS mutant positive, and 21 patients (60%) were RAS mutant negative. The most frequently reported study drug-related events at RP2D were diarrhea (31%), nausea (20%), increased creatinine (17%), vomiting (9%), and rash (5%). All bone marrow biopsies in Part 1 showed less than partial response. In Part 2, one patient with RAS (+) AML, had complete remission with

Study Type	Study Identifiers	Status/Results
		incomplete platelet recovery (CRp) at two sequential visits. A second patient with RAS (-) AML, had a complete response (CR) on cycle 2, day 1. All other evaluations in Part 2 AML patients showed less than partial response (PR). A third patient with RAS (+) MDS had a PR on cycle 2, day 1. All other bone marrow evaluations in Part 2 MDS patients showed less than PR.
Commercial sponsored	NCT02994732 BVD-523HV001 A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C] BVD-523 Following Single Oral Dose Administration in Healthy Male Subjects	The purpose of study BVD-523HV001 was to evaluate the absorption and excretion characteristics as well as relevant pharmacokinetic properties of ulixertinib; and to characterize and, where possible, identify the metabolites present in plasma, urine, and feces in healthy male subjects following a single dose of 600mg (approximately 200 µCi) of [14C]-ulixertinib. The secondary objective of this study was to evaluate the safety and tolerability of a single oral dose of [14C]-labeled ulixertinib in healthy male subjects. A total of 6 subjects were enrolled. The absorption of ulixertinib (BVD-523) was moderate and after reaching Cmax, concentrations of ulixertinib (BVD-523) in plasma appeared to decline in a generally biphasic manner. Ulixertinib (BVD-523) undergoes moderate metabolism to produce 13 identified/characterized metabolites in plasma and excreta. The metabolites BVD-502+BVD503 and BVD-513 were formed moderately rapidly and their plasma concentration-time profiles generally mirrored that of parent drug, suggesting formation rate limited elimination. The metabolite BVD-506 was found to be present and disproportionate levels compared to levels measured in pre-clinical in vivo studies. The primary route of elimination was through fecal excretion. No clinically significant findings with respect to clinical laboratory, vital signs, electrocardiogram (ECG), or physical examinations. Fatigue and diarrhea were reported for 2 subjects (33%) and were possibly related to study drug. All treatment-emergent AEs (TEAEs) were of mild severity and there were no moderate or severe events reported.
Commercial sponsored	BVD-523A-FE A Randomized, Open-Label, Single-Dose, 2-Way Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics, Safety and Tolerability of Orally Administered BVD-523 in Healthy Volunteers	A Phase I, randomized, open-label, single-dose, 2-way crossover study to assess the safety and PK in 14 healthy male and female subjects. Subjects received a single oral dose of BVD-523A (an investigational formulated blend of ulixertinib) in 2 different treatment periods; once after an overnight fast of at least 10 hours and once after consumption of an FDA-defined high-fat breakfast. There was a washout period of 5 days between dosing in one period and dosing in the next period. Subjects were randomized equally to receive 1 of 2 treatments sequences (fasted/fed or fed/fasted), with 7 subjects assigned to each sequence. Each subject received both treatments. Pharmacokinetic (PK) concentrations achieved in the fed group were considerably higher than observed in the fasted group. However, fasting and fed conditions were extreme. Collective experience in patients and healthy volunteers shows that best exposure and variability is achieved when ulixertinib is taken with food. There were no clinically significant findings with respect to clinical laboratory, vital signs, ECG, or physical examination. Headache in 2 subjects (14%) under fed conditions and diarrhea in 1 subject (7%)

Study Type	Study Identifiers	Status/Results
		under fasted conditions were considered by the investigators to be possibly related to the study drug. All TEAEs were of mild severity, and there were no moderate or severe events reported.
Commercial sponsored	BVD-523-FC A Randomized, Open-Label, Single-Dose, 2-Way Crossover Study Evaluating the Pharmacokinetics, Safety, and Tolerability of two oral formulations of Ulixertinib (BVD-523) in Healthy Volunteers	A Phase I, randomized, open-label, single-dose, 2-way crossover study to assess the effect of two oral formulations of ulixertinib on the PK, safety, and tolerability of a single oral dose of 600mg ulixertinib in 14 healthy male and female subjects. The oral formulations included a single dose of 600mg powder in capsule (PIC) formulation and a single oral dose of 600mg formulated blend formulation of ulixertinib. Subjects were randomized equally to receive 1 of the 2 treatment sequences with 7 subjects assigned to each sequence and a washout period of 5 days separated the treatments. The formulated blend formulation produced peak and total systemic exposures which were slightly lower than PIC formulation. Additionally, the AUC_{last} and AUC_{inf} of the formulated blend formulation were approximately 25% lower than compared to PIC formulation. No clinically significant findings with respect to clinical laboratory, vital signs, ECGs, or physical examinations. Headaches were reported in 4 subjects (29%) and were possibly related to study drug. All other possibly related TEAEs were only reported by 1 subject (7%). All events were of mild severity, except for 1 event of urticaria, which was of moderate severity.
Commercial sponsored	NCT04488003 BVD-523-ABC A Two-Part, Phase II, Multi-center Study of the ERK Inhibitor Ulixertinib (BVD-523) for Patients with Advanced Malignancies Harboring MEK or Atypical BRAF Alterations	Ongoing
Investigator sponsored	NCT02608229 Phase Ib Study of BVD-523 Plus Nab-Paclitaxel and Gemcitabine in Patients with Metastatic Pancreatic Cancer	Study was stopped after part 1 (dose escalation) due to tolerability issues experienced from the triple combination treatment.
Investigator sponsored	NCT03454035 A Phase I Trial of Ulixertinib (BVD-523) in Combination with Palbociclib in Patients with Advanced Solid Tumors with Expansion Cohort in Previously Treated Metastatic Pancreatic Cancer	Ongoing
Investigator sponsored	NCT04145297 Phase 1 study of ulixertinib and hydroxychloroquine in patients with advanced MAPK-mutated	Ongoing

Study Type	Study Identifiers	Status/Results
	gastrointestinal adenocarcinomas	
Investigator sponsored	NCT03417739 A Phase II Study of BVD-523 in Metastatic Uveal Melanoma	In interim analysis of 13 patients, 4 patients had best response of stable disease (SD) (31%), 7 had best response of progressive disease (54%), and 2 were unevaluable for response (15%). According to the Simon design, the trial stopped recruitment at this point due to lack of responders in the first stage.
Investigator sponsored	NCT04566393 Expanded Access to Ulixertinib (BVD-523) in Patients with Advanced MAPK Pathway-Altered Malignancies	Ongoing
NCI sponsored	NCT03155620 Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial)	Ongoing
NCI sponsored	NCT02465060 Targeted Therapy Directed by Genetic Testing in Treating Patients with Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial)	Ongoing
NCI sponsored	NCT03698994 Ulixertinib in Treating Patients with Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders with MAPK Pathway Mutations (A Pediatric MATCH Treatment Trial)	Ongoing

4.5.3 Hydroxychloroquine

Hydroxychloroquine is an old drug originally approved for the treatment and prevention of malaria. While the exact mechanism of action is still not well understood, it has been shown to inhibit lysosomal acidification and prevent the degradation of autophagosomes. This inhibition suppresses the process of autophagy, the cellular survival mechanism.

Due to extensive distribution and protein binding after absorption, hydroxychloroquine has a long half-life ranging from 40-50 days. 40-50% of the drug is excreted renally and 24-25% eliminated through the feces.

Hydroxychloroquine has a known risk for QT interval corrected (QTc) prolongation and Torsades de Pointes (TdP). Therefore, caution should be used when administering other medications of TdP risk. Refer to the package insert for more information.

4.5.4 Dose Rationale

Hydroxychloroquine has been FDA approved for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis at doses ranging from 200 mg to 600 mg daily. Due to the increased risk of retinopathies, it is recommended not to exceed 600 mg daily for long term maintenance. However, it is only with chronic exposure that retinopathies are observed. The rate of retinopathies dramatically increases after 5 years of hydroxychloroquine use and a cumulative dose of over 1000 g (total).[31] Multiple trials have conducted investigations of 600 mg twice-daily dosing for the treatment of cancers and have found the dose safe and tolerable. [32-34] Wolpin et al. found similar adverse event profiles between 400 mg and 600 mg twice-daily dosing of single-agent hydroxychloroquine in pancreatic cancer patients.[34] At this dose level, it would take approximately 2.25 years to reach a total accumulated dose of 1000 g. It is not anticipated that patients will exceed 12 months of treatment while on this trial. Therefore, due to the relatively short-term use of hydroxychloroquine and the similar adverse event profile, 600 mg twice-daily dosing will be utilized for the study combination.

Ulixertinib (first-in-class ERK1/2 inhibitor) has been tested in a rapid phase I dose-escalation and expansion study that enrolled 135 patients. Doses from 10 to 900 mg twice daily were explored and the recommended phase 2 dose of 600 mg twice daily was found. It was well tolerated, and all toxicities were manageable and reversible. The most common treatment-related AEs were diarrhea, fatigue, nausea, and dermatitis acneiform. In this monotherapy setting including a diverse patient population, about 14% of the response evaluable patients dosed at or above the MTD experienced a partial response (PR). Patients demonstrating a response included NRAS, $BRAF^{V600}$, and $BRAF^{non\text{-}V600}$ mutant solid tumors. [35]

In an expanded access protocol, ulixertinib is used to treat patients with advanced MAPK pathway-altered malignancies (NCT04566393). At the time of this protocol submission, 9 patients have received the combination of ulixertinib (dose ranges of 300 – 450 mg BID) and hydroxychloroquine (dose ranges of 200 – 600 mg BID). The dose of ulixertinib 450 mg BID combined with hydroxycholorquine 600 mg BID has been used to treat 4 of those patients with 2 of those patients on treatment for 21 and 39 days. The safety profile observed in these patients receiving this combination has been similar to the safety profile of the individual agents.

In the phase I, dose-escalation trial ulixertinib was safely combined with hydroxychloroquine (NCT04145297) in a 6-patient cohort at 450 mg BID and 600 mg BID, respectively. There were 6 AEs, but only 2 were considered related to ulixertinib and no SAEs were reported. One patient experienced grade 1 fatigue and another patient experienced grade 3 QT prolongation. The event of QT prolongation was considered probably related to both hydroxychloroquine and ulixertinib, and the patient had both drugs held until resolution. The patient was subsequently restarted on full dose ulixertinib and hydroxychloroquine at a reduced dose level of 800mg QD.

4.5.5 Drug-Drug Interaction Assessment

Based on the characteristics of each ulixertinib and hydroxychloroquine, drug-drug interaction (DDI) potential among ulixertinib and hydroxychloroquine exists for the following reasons:

- *In vitro,* human liver microsome studies demonstrate ulixertinib to induce CYP1A2, CYP2B6, and CYP3A4 mRNA expression, whilst also directly inhibiting CYP2C8 and CYP3A4/5.

- Hydroxychloroquine is metabolized by CYP3A4.

However, the DDI potential may be limited for the following reasons:

- No significant CYP induction was observed after up to 14 days of ulixertinib treatment in rats.
- The drugs do not share metabolic or elimination pathways except for CYP3A4:

    - Ulixertinib is metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and extensively eliminated in feces.

    - Hydroxychloroquine is metabolized by CYP3A4 and is primarily excreted renally.

While both medications are metabolized by CYP3A4, ulixertinib has the option for metabolism by multiple alternative CYP enzymes. Ultimately DDI potential will be defined by pharmacokinetic evaluations of ulixertinib and hydroxychloroquine administered at a tolerated combination dose in treated patients.

4.5.6 Clinical Experience

Hydroxychloroquine, the most widely used autophagy inhibitor, has been safely combined with multiple anti-cancer therapies in the past and these trials have generated preliminary data to support the theory that an autophagy inhibitor could overcome acquired therapeutic resistance.[32,33,36,37] Hydroxychloroquine is also currently under investigation in combination with the MEK inhibitor, trametinib, and has been well tolerated (NCT03825289).

In the phase 1b dose-escalation portion of the ulixertinib combined with palbociclib trial (NCT03454035), an MTD was achieved at the doses of ulixertinib 450mg BID combined with palbociclib 125 mg daily. This combination dose demonstrated SD in 3 patients, one of which with metastatic pancreatic cancer remained on study for over 12 months. The PK analysis for ulixertinib and palbociclib was linear and consistent with previously published data. One grade 3 hyponatremia was reported in this dose combination and three patients demonstrated stable disease with one patient remaining on study for over 12 cycles.

5 OBJECTIVES AND ENDPOINTS

5.1 Primary Objectives

- To assess the safety and tolerability of ulixertinib and hydroxychloroquine in patients with advanced, RAS, non-V600 BRAF, MEK1/2 (MAP2K1/2), or ERK1/2 (MAPK3/1) mutated gastrointestinal malignancies.

  Primary endpoint: The incidence and frequency of adverse events (AEs) and serious adverse events (SAEs) characterized by type, severity (as defined by the NCI CTCAE, version 5.0), seriousness, duration, and relationship to study treatment.

- To assess the efficacy of ulixertinib and hydroxychloroquine in patients with advanced, RAS, non-V600 BRAF, MEK1/2 (MAP2K1/2), or ERK1/2 (MAPK3/1) mutated gastrointestinal malignancies.

  Primary Endpoint: Overall response rate as defined by the proportion of patients achieving a confirmed partial response or complete response (CR) [defined by RECIST 1.1] as evaluated by the local treating investigator.

5.2 Secondary Objective

- To assess the duration of efficacy of ulixertinib and hydroxychloroquine in patients with advanced, RAS, non-V600 BRAF, MEK1/2 (MAP2K1/2), or ERK1/2 (MAPK3/1) mutated gastrointestinal malignancies.

  Secondary Endpoint: Progression-free survival (PFS) as defined as the time from study drug initiation to the time of documented disease progression (as assessed by RECIST 1.1) or death from any cause.

5.3 Exploratory Objective

- To evaluate the bioactivity of ulixertinib and hydroxychloroquine against ERK1/2 (MAPK3/1), autophagy pathways, and pharmacodynamic biomarkers.

  Exploratory Endpoint:

  - Pharmacokinetics of ulixertinib and hydroxychloroquine
  - Blood and/or tissue samples used to assess biomarkers (RPPA, Nanostring, ctDNA are assays planned but not limited to only these)

6 STUDY DESIGN

6.1 Overall Design

This is an open-label, multicenter, phase 2 basket study of ulixertinib in combination with hydroxychloroquine in patients with advanced gastrointestinal malignancies harboring RAS, non-V600 BRAF, MEK1/2, or ERK1/2 mutations. The trial will have five baskets based on disease primary as listed below.

- Basket 1: Cholangiocarcinoma including intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, or extrahepatic cholangiocarcinoma;
- Basket 2: Pancreatic adenocarcinoma;
- Basket 3: Colorectal adenocarcinoma;
- Basket 4: Esophageal adenocarcinoma, esophageal squamous cell carcinoma, or gastroesophageal junction (GEJ) adenocarcinoma;
- Basket 5: Gastric adenocarcinoma.

To assess eligibility, cancer mutational status must be confirmed through patient medical records by treating physician. Once deemed eligible, ulixertinib and hydroxychloroquine will be orally administered twice daily on 28-day cycles. Safety will be assessed regularly through the monitoring of AEs, laboratory values, physical exams, vital signs, echocardiogram, eye exams, and ECGs. Disease assessments will be performed regularly as well to assess treatment efficacy. Upon disease progression, patients will be followed for safety.

While the overall trial is a basket design, each individual basket will operate using a Simon two-stage design independently of the other baskets.

The first stage in each basket will open to enrollment and remain open until 13 patients are declared evaluable for response, at which time enrollment will be placed on hold for the evaluation of efficacy. To be evaluable for this stage 1 efficacy analysis, a patient must have completed at least one cycle of therapy and must have at least 75% of the prescribed doses of ulixertinib and hydroxychloroquine during cycle 1. Non-evaluable patients may remain on study treatment if deemed to be clinically benefiting by the treating Investigator.

The stage 1 efficacy analysis will occur when all evaluable patients have had at least one post-treatment disease evaluation or have discontinued study treatment due to clinical progressive disease or drug-related AEs. Patients who have discontinued study treatment due to clinical progressive disease or drug-related AEs prior to the first efficacy evaluation will be considered non-responders. If a patient in the first 13 evaluable patients has an unconfirmed partial or complete response but has not yet had a confirmatory scan at the time of the stage 1 efficacy analysis, that patient may be counted as a responder for the purposes of the Stage 1 evaluation. If ≥ 4 of the first 13 evaluable patients in stage 1 have a complete or partial

response, with permission of the Safety Monitoring Committee (SMC) the sponsor may open enrollment to stage 2 for that basket. Stage 2 will expand enrollment of each basket until a total of 43 patients, including those enrolled during stage 1, have been enrolled. Any patient deemed non-evaluable for the primary efficacy endpoint may be replaced.

An internal SMC will be charged with assuring risk/benefit balance for patients involved in the study. They will make study conduct recommendations based on emerging safety and efficacy data. Stage 2 of enrollment on each basket will not open until data review and approval from the SMC.

6.2 Number of Patients

Total enrollment for stage 1 is targeted at approximately 65 patients with 13 patients per group. Additional patients may be enrolled as appropriate.

Total enrollment for stage 2 is targeted to approximately 150 patients with up to 30 patients per group. Additional patients may be enrolled as appropriate.

6.3 Number of Study Sites

The study will take place at sites within the United States. Approximately 10 sites will be utilized, however, additional sites may be added. Clinical trial networks may be utilized. Each study site may enroll as many eligible patients as possible.

6.4 End of Study

As the primary endpoint of the study is overall response, a patient is considered to have completed the study upon disease progression or death, whichever comes first.

The study will end when the last patient remaining on study has disease progression per RECIST 1.1, initiates subsequent anti-cancer therapy, or dies, whichever occurs first. In addition, the sponsor may terminate the study at any time. If the sponsor terminates the study, all effort will be made to ensure continued access to study treatment for any patients receiving clinical benefit from the study intervention.

7 STUDY POPULATION

Potential study participants must meet all inclusion criteria and no exclusion criteria to be deemed eligible for trial participation. To ensure patient safety, all patients must be deemed eligible at the time of study registration and must continue to meet eligibility criteria up to cycle 1 day 1 dosing.

7.1 Inclusion Criteria

1. Male or female patient aged ≥ 18 years.

2. Histologically confirmed esophageal adenocarcinoma, esophageal squamous cell carcinoma, GEJ adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, extrahepatic cholangiocarcinoma, or colorectal adenocarcinoma harboring a MAPK-mutated GI malignancy: KRAS, NRAS, HRAS, BRAF non-V600, MEK1/2 (MAP2K1/2), or ERK1/2 (MAPK3/1).

3. Patients must have been previously treated with one or more lines of anti-cancer therapy and have documented disease progression during or after their most recent line of anti-cancer treatment subject to the restrictions below (variations of standard of care may exist and are acceptable):
    - Patients with intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, or extrahepatic cholangiocarcinoma who have progressed during or after receiving a first-line regimen of gemcitabine/cisplatin unless deemed ineligible by the treating investigator to receive gemcitabine/cisplatin regimens due to prior comorbidities. Patients who are currently stable on second-line or beyond regimens but, in the opinion of the investigator have become intolerant to current treatment are also eligible for trial participation.

    - Patients with pancreatic adenocarcinoma must have progressed during or after first-line therapy of FOLFIRINOX/ mFOLFIRINOX, or gemcitabine/nab-paclitaxel unless deemed ineligible by the treating investigator to receive chemotherapy-based regimens due to prior comorbidities.

    - Patients with colorectal adenocarcinoma must have progressed during or after two lines of therapy, including FOLFOX ± Avastin and FOLFIRI ± Avastin, unless deemed ineligible by the treating investigator to receive chemotherapy-based regimens due to prior comorbidities.

    - Patients with esophageal adenocarcinoma, esophageal squamous cell carcinoma, GEJ adenocarcinoma, or gastric adenocarcinoma who have progressed during or after their first two lines of therapy. Patients who are currently stable on second-line or beyond regimens but, in the opinion of the investigator, have become intolerant to current treatment are also eligible for trial participation.

        - Acceptable first-line regimens: FOLFOX, 5-FU/Cisplatin, FOLFIRI, Paclitaxel/Cisplatin or Carboplatin, Docetaxel/Cisplatin, DCF (or modifications thereof), or ECF (or modifications thereof) unless deemed ineligible by the treating investigator to receive chemotherapy-based regimens due to prior comorbidities.

        - Acceptable second-line regimens: Ramucirumab/Paclitaxel, Docetaxel, Paclitaxel, Irinotecan, Trifluridine/Tipiracil, or FOLFIRI,

unless deemed ineligible by the treating investigator to receive chemotherapy-based regimens due to prior comorbidities.

- Patients with dMMR/MSI-H tumors must have progressed during or after immunotherapy.

4. Measurable disease by RECIST 1.1 criteria by CT or Magnetic resonance imaging (MRI).

5. Willing to provide a biopsy at the time points indicated on the Schedule of Activities.

6. ECOG Performance Status ≤ 1.

7. Adequate organ function as defined as:

    - Hematologic:
        - Absolute neutrophil count (ANC) ≥ 1500/mm^3
        - Platelet count ≥ 100,000/mm^3
        - Hemoglobin ≥ 9 g/dL
    - Hepatic:
        - Total Bilirubin ≤ 1.5x institutional upper limit of normal (ULN)
        - AST(SGOT)/ALT(SGPT) ≤ 3 × institutional ULN
            - Patients with liver metastases will be allowed to enroll with AST and ALT levels ≤ 5 x ULN.
    - Renal:
        - Estimated creatinine clearance (CL_{cr})≥ 50 mL/min by Cockcroft-Gault formula:
            - Males: $\frac{(140-age) \times weight\ [kg]}{serum\ creatinine\ \left[\frac{mg}{dL}\right] \times 72}$
            - Females: $\left(\frac{(140-age) \times weight\ [kg]}{serum\ creatinine\ \left[\frac{mg}{dL}\right] \times 72}\right) \times 0.85$

8. For female patients: Negative serum pregnancy test within 72 hours prior to first dose of study drugs for women of childbearing potential. The following definitions apply:

    - Women of childbearing potential, defined as a sexually mature woman:

- Has not been naturally post-menopausal for at least 12 consecutive months (i.e., who has had menses anytime in the preceding 12 consecutive months).
- Has not undergone menopause, surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women not of childbearing potential:
  - Amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, if any.
  - Underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

9. Male and female patients of childbearing potential agree to use highly effective contraception throughout the study and at least 90 days after the last study treatment administration (see Section 7.3.1).

10. Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to any prior cancer therapy, unless considered clinically not significant by the treating investigator.

11. Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

7.2 Exclusion Criteria

1. Received systemic antineoplastic therapy (including unconjugated therapeutic antibodies and toxin immunoconjugates) or any investigational therapy ≤ 14 days or within five half-lives prior to starting study treatment, whichever is shorter.

2. Received radiotherapy ≤ 14 days prior to the first dose of study treatment.

   Note: Localized radiation therapy for the treatment of symptomatic bone metastasis is allowed during that timeframe.

3. Undergone major surgery ≤ 3 weeks prior to starting study drug or who have not fully recovered from major surgery.

4. The diagnosis of another malignancy within ≤ 3 years before study enrollment, except for those considered to be adequately treated with no evidence of disease or symptoms and/or will not require therapy during the study duration (e.g., basal cell or squamous cell skin cancer, carcinoma in situ of the breast, bladder or of the cervix, or low-grade prostate cancer with Gleason Score ≤ 6).

5. Known uncontrolled brain metastases or cranial epidural disease.

Note: Patients with stable brain metastases/cranial epidural disease either treated or being treated with a stable dose of steroids (<20 mg of prednisone daily or equivalent) or anticonvulsants, with no dose change within 4 weeks before the first study drug dose, and no anticipated dose change, are eligible. In the event of steroid taper post-radiation therapy, taper must be complete within 2 weeks before baseline.

6. History or current evidence of central serous retinopathy (CSR) or retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity).

7. Current evidence of uncontrolled, significant intercurrent illness including, but not limited to, the following conditions:

    - Cardiovascular disorders:
        - Congestive heart failure (CHF) New York Heart Association Class 3 or 4, unstable angina pectoris, serious cardiac arrhythmias.
        - Stroke (including transient ischemic attack [TIA]), myocardial infarction (MI), or other ischemic events, or thromboembolic event (eg, deep venous thrombosis, pulmonary embolism) within 3 months before the first dose.
        - QTc prolongation defined as a QTcF >470ms.
        - Known congenital long QT.
        - Left ventricular ejection fraction < 50%.
    - History of seizures.
    - Impairment of gastrointestinal function or gastrointestinal disease (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
    - Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures (e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, [patients may not receive the drug through a feeding tube], social/ psychological issues, etc.)

8. Prior stomach or duodenal resection that in the opinion of the Principal Investigator and Medical Monitor would affect the breakdown and absorption of the study medications. A patient with a feeding tube should also be excluded, as ulixertinib capsules cannot be taken apart.

Note: Ulixertinib is primarily absorbed in the duodenum and therefore patients with any prior stomach or duodenal resection should be discussed with the Medical Monitor.

9. Known Human immunodeficiency virus (HIV) infection with a detectable viral load within 6 months of the anticipated start of treatment.

   Note: Patients on effective antiretroviral therapy with an undetectable viral load within 6 months of the anticipated start of treatment are eligible for this trial.

10. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination, radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C.

    Note: Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11. Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.

12. Known prior severe hypersensitivity to investigational product (IP) or any component in its formulations (NCI CTCAE v5.0 Grade ≥ 3).

13. Patients taking prohibited medications as described in Section 8.7.2. A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur before the start of treatment.

7.3 Lifestyle Considerations

7.3.1 Contraception

Ulixertinib has not undergone testing in pregnant women, but because of known embryotoxic and abortifacient risk associated with MAPK inhibition, women of childbearing potential and men with partners of childbearing potential must exercise appropriate contraception to avoid pregnancy. Highly effective contraception must be used for the duration of study treatment and 90 days after the last dose of study drug.

Male patients must agree to use a condom (even after vasectomy) during treatment and for 90 days after the last dose of study treatment. In addition, female partners of childbearing potential should also use a highly effective contraceptive method during the same time period.

Acceptable highly effective contraceptive methods include:

- Bilateral tubal occlusion

- Vasectomized partner
- Intra-uterine device (IUD) or hormone-releasing system (IUS)
- Any hormonal (estrogen combined with progesterone or progesterone alone) contraception associated with inhibition of ovulation: implanted, oral, intravaginal, transdermal, or injectable
- The combination of spermicide with a compatible barrier method (i.e. diaphragm, sponge, or male or female condoms)
- Abstinence from heterosexual intercourse

7.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but who do not meet one or more criteria required for participation in the trial during the screening procedures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened (up to a maximum of 1 time for the same individual). Rescreened patients will be assigned a new patient identification number. Labs can be retested within the screening window and not count as a rescreen.

7.5 Strategies for Recruitment

Patients will be recruited at sites around the United States. Site Principal Investigators will be responsible for the recruitment of eligible patients from their local clinics and communities.

8 STUDY DRUGS

8.1 Dosing and Administration

Ulixertinib and hydroxychloroquine will be administered twice-daily on a 28-day cycle starting with cycle 1 day 1. Ulixertinib and hydroxychloroquine will be administered orally twice daily (every 12 hours ± 2 hours) together with food. Patients will be instructed to take the medications at approximately the same time every day.

Patients should be instructed to swallow the study drug whole and not chew the capsule before swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should not take extra medication for any reason. A patient that is observed to vomit an intact capsule after dosing in the clinic during the PK measurements may receive a substitute dose of drug. However, patients should be instructed NOT to take a substitute capsule if

vomiting occurs after self-dosing at home. Missed doses should be skipped and not taken as a double dose at the next dosing timepoint.

Patients will be provided enough ulixertinib and hydroxychloroquine for a full cycle to self-administer at home.

8.1.1 Study Drug Compliance

The Investigator will dispense the study drugs only for use by patients enrolled in the study as described in this protocol in the SOA (Table 1). The study drugs are not to be used for reasons other than those described in this protocol.

The Investigator or other study staff will supervise study drug treatment given in the clinic and instruct the patient on study drug self-administration. Patients will be asked to bring their study drug containers with them at the start of each cycle and compliance with protocol-defined study drug intake will be checked by pill count. In case of non-compliance, the patients will be instructed again on how to appropriately take study drug.

Information pertaining to study drug compliance (i.e., date time, and dose) will be recorded in the electronic case report form (eCRF) by the study team. A member of the study team will review patient drug compliance at the end of each cycle and provide patient re-education as required. Any reason for non-compliance will be clearly documented in the patient's research chart and the corresponding eCRF. At the discretion of the Principal Investigator, a patient may be discontinued from the trial for non-compliance with study visits or study drug.

Patients will be required to return any unused medication or empty bottles at the end of every cycle. Unless prohibited by investigational site's SOP, used study drug is to be retained until the monitor has verified drug accountability. Once the site monitor has verified drug accountability at the site, any drug remaining in opened dispensing containers will be destroyed. Unused and unopened study drug will be returned to the Sponsor.

The total number of capsules dispensed, returned, and documented as taken will be reconciled to support drug accountability. Treatment compliance will be calculated and recorded separately for each drug. It will be recorded as a percentage defined as the number of doses taken divided by the expected number of doses taken multiplied by 100%.

8.2 Investigational Product Supplies

BioMed Valley Discoveries, Inc. will provide both investigational products, ulixertinib and hydroxychloroquine. Product labeling and packaging will be in accordance with Good Manufacturing Practice (GMP) and applicable regulatory requirements. The investigator or appropriately trained and delegated personnel shall ensure appropriate accounting is maintained demonstrating receipt, distribution, and destruction of both investigational products. They should also ensure appropriate storage, handling, and distribution of the investigational products according to the protocol and any applicable laws and regulations.

8.2.1 Preparation and Dispensing

The investigator or appropriately trained and delegated personnel will prepare and dispense all investigational supplies. The investigational products will be supplied only to patients deem eligible for study treatment. IP may not be dispensed to patients who have not been enrolled in the trial.

8.2.2 Ulixertinib

Ulixertinib drug substance is manufactured according to cGMP as a monohydrochloride salt and is supplied as a formulated powder blend comprised of standard excipients to support the manufacturing processes that is encapsulated in a hard gelatin capsule. Capsules (white) contain 150 mg of ulixertinib calculated on free base content and are packaged in white high-density polyethylene (HDPE) bottles.

8.2.3 Hydroxychloroquine

Hydroxychloroquine will be supplied as sulfate tablets which are white, to off-white, film-coated tablets. Each tablet contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base). Each bottle will contain 100 tablets and will be appropriately labeled according to regulations.

8.2.4 Product Storage and Stability

Information will be provided in the pharmacy manual.

8.3 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the dose modification recommendations (Table 5). Doses of any investigational product that were not administered due to toxicity will not be replaced within the same cycle. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on the dose modifications recommendations. If toxicities require dose hold, both study drugs should be held and resumed concurrently. If a patient experiences a dose interruption, the SOA remains fixed according to cycle 1 day 1 (note that assessments that require a patient to be at steady-state and safety evaluations that are dose-dependent (ECG)), should be performed following the resumption of therapy).

If a toxicity-related dose delay lasts for > 21 days, treatment will be discontinued permanently, and the patient should be removed from study treatment. If a patient requires a dose hold for > 21 days for a non-treatment related adverse event or situation (i.e. radiation therapy) the patient may continue on study only after approval and discussion with the Sponsor and Medical Monitor.

8.4 Dose Reductions

Following dosing interruption due to treatment-related toxicity, the offending agent may need to be resumed at a reduced dose as per the dose modification recommendations. Ulixertinib and hydroxychloroquine may be independently modified as necessary to address the emergence of

treatment-related toxicities. Dose reduction should proceed by decreasing the administered dose of the offending agent by one dose level per Table 5.

Once the study treatment has been reduced for a given patient, all subsequent cycles will be administered at that dose level. Intra-patient dose re-escalation is not allowed except as described in the toxicity management guidelines, Table 6.

Table 5: Ulixertinib and Hydroxychloroquine Dose Levels

Dose Level	Ulixertinib
Dose Level 0	450 mg twice daily
Dose Level -1	300 mg twice daily
Dose Level -2	150 mg twice daily

Dose Level	Hydroxychloroquine
Dose Level 0	600 mg twice daily
Dose Level -1	800 mg daily

8.5 Dose Modifications Guidelines

Patients experiencing AEs attributed to either study drug may undergo dose modifications for toxicity management; however, the ultimate decision is up to the investigator's discretion. Dose modification guidelines are provided below for AEs considered to be related to either study drug. If either ulixertinib or hydroxychloroquine requires a reduction below Dose Level -2 or Dose Level -1, respectively, for toxicity management, study treatment will be discontinued.

Table 6: Treatment-related adverse event management guidelines

Adverse Event	Severity	Adverse Event Management
Hematologic Toxicities		
Anemia	Grade ≥ 3	• Hold study treatment and monitor weekly. • Once resolved to grade ≤ 1, resume study treatment. • The doses of ulixertinib and hydroxychloroquine may be reduced by one dose level.
Neutropenia with or without fever	Grade ≥ 3	• Hold study treatment and monitor weekly. • Once resolved to grade ≤ 1, resume study treatment. • The doses of ulixertinib and hydroxychloroquine may be reduced by one dose level.
Thrombocytopenia	Grade ≥ 3	• Hold study treatment and monitor weekly. • Once resolved to grade ≤ 1, resume study treatment. • The doses of ulixertinib and hydroxychloroquine may be reduced by one dose level.
Non-Hematologic Laboratory Toxicities		
Any clinically significant non-hematologic laboratory abnormality.	Grade ≥ 3	• Hold study treatment. • Resume once resolved to grade ≤ 1 or baseline. Reduce the offending agent(s) (as assessed by the treating investigator) by one dose level upon the continuation of therapy.
	Grade ≥ 4	• Consider permanently discontinuing, after discussion with medical monitor.
Cutaneous Reactions		
Rash (maculopapular or acneiform)	Grade 1	• Continue study treatment and closely monitor. • Consider topical steroid cream BID, clindamycin gel, oral antihistamine. • Reassess after 2 weeks.

	Grade 2	• Continue study treatment and closely monitor. • Consider oral antihistamine and/or oral steroids (prednisone 0.5mg/kg or equivalent) for maculopapular rash. • Consider doxycycline. • Reassess after 2 weeks. If no improvement, interrupt dosing until grade ≤ 1. Once resolved, resume ulixertinib at a reduced dose level or same dose with close observation.
	Grade ≥ 3	• Hold study treatment, initiate treatment, and maintain close monitoring. • Use moderate strength topical steroids PLUS oral steroids (prednisone 0.5mg/kg or equivalent); consider adding oral antibiotics as described for Grade 2. • Consider dermatologist consult. • If rash resolves to grade ≤ 1, restart study drugs, with ulixertinib reduced by one dose level. • Escalation of ulixertinib to the previous dose level may be permitted following discussion with the medical monitor. • If no recovery to grade ≤ 1 within 3 weeks, consider discontinuation of ulixertinib and hydroxychloroquine permanently.
Photosensitivity	Grade ≥ 3 lasting > 7 consecutive days despite treatment (as per local practice)	• Hold study treatment. • Continue study treatment upon resolution to grade ≤ 1. Reduce hydroxychloroquine by one dose level upon resolution.
Stevens-Johnson syndrome or toxic epidermal necrolysis	Any	• Hold study drugs. • Obtain dermatology consult. • Consider permanent discontinuation of study treatment after discussion with medical monitor.
Gastrointestinal Toxicities		
Diarrhea	Grade ≤ 2	• Continue study treatment.

		• Initiate symptom management and supportive care (i.e. loperamide and hydration).
	Grade ≥ 3	• Hold study treatment. • Initiate symptom management and supportive care (i.e. loperamide and hydration). • Upon resolution to grade ≤ 1 or baseline for > 24 hours, restart study treatment and reduce ulixertinib and hydroxychloroquine by one dose level. • Escalation of ulixertinib to the previous dose level is allowed in the absence of another episode of grade ≥ 3 diarrhea in the 4 weeks after dose reduction.
Nausea or vomiting lasting ≥ 7 days despite optimal medicinal therapy.	Grade ≥ 3	• Hold study treatment and monitor until resolution to grade ≤ 1. • Resume once resolved to grade ≤ 1. • The dose of ulixertinib and hydroxychloroquine may be reduced by one dose level.
Hepato-biliary Toxicities		
ALT/AST increase	Grade 2	• Hold study treatment and evaluate for other causes. • Upon resolution to grade <1 ulixertinib and hydroxychloroquine may be resumed at a reduced level.
	Grade 3 or 4	• Hold study treatment and evaluate for other causes. • Consider GI consult. • Upon resolution to grade < 1 continued study treatment should be discussed with the medical monitor. • If study treatment is resumed (grade must have resolved to <1) ulixertinib and hydroxychloroquine should be resumed at a reduced level.
Ophthalmological Toxicities		

Retinal vein occlusion, retinal detachment, vitreal detachment, cataract or clinically relevant ocular event	Any	• Hold study treatment. • Obtain ophthalmology consult and follow up until resolution/stabilization. • Upon resolution to baseline, discuss with medical monitor regarding re-initiation of study treatment; decrease dosing of ulixertinib and hydroxychloroquine by one dose level.
Cardiac Toxicity		
QTc interval prolongation	Grade 3 (mean from triplicate ECG)	• Hold study treatment. • Upon resolution to grade ≤ 1, resume study treatment and decrease the dose of hydroxychloroquine. • If reoccurs, discontinue study treatment.
Symptomatic congestive heart failure	Any	• Consider permanently discontinuation of study treatment after discussion with medical monitor.
All Other AEs		
All other clinically significant AEs except: • Nausea, vomiting, or diarrhea lasting ≤ 72 hours; • Fatigue lasting < 5 days; • Hypertension controlled with medical therapy.	Grade ≥ 3 or unacceptable toxicity	• Hold study treatment. • Monitor AE until resolution to Grade ≤ 1. • Resume study treatment upon resolution and reduce the dose of the offending agent (as assessed by the treating investigator) by one dose level.

Abbreviations: AE = adverse event; BID = bis in die (twice daily); ECG = electrocardiogram; GI = gastrointestinal.

8.6 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study as deemed necessary by the treating investigator. Granulocyte-colony stimulating factors may be used at any time according to the current American Society of Clinical Oncology (ASCO) guidelines for the management of treatment-emergent neutropenia. The use of hematopoietic growth factors is at the discretion of the treating physician and according to local institutional standards.

Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

8.7 Concomitant Medications and Therapies

All administered concomitant medications (including herbal supplements) and non-medicinal therapies (including transfusions) used 28 days prior to cycle 1 day 1, and until 30 days after the last dose of study treatment will be recorded in the patient's research chart and corresponding eCRF. All medications, including those used to treat AEs, chronic conditions or diseases, or as supportive therapy should be documented in the eCRF.

8.7.1 Radiotherapy

If deemed necessary by the treating investigator and reviewed by the medical monitor, palliative radiation therapy for a single site (e.g., bone or brain metastasis) is allowed provided that it is the only site of disease progression. The radiation field must not affect any of the target lesions designated for disease assessment. Protocol treatment will be held during radiation therapy and will be restarted after any acute toxicities have resolved following the conclusion of therapy.

8.7.2 Prohibited Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the active treatment period. Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy;
- Other investigational agents;
- Radiation therapy (with the exception noted above);
- Any live-attenuated vaccine therapies for the prevention of infectious disease (e.g. MMR, nasal flu, or rotavirus);
- Herbal remedies known to potentially interfere with major organ function (e.g. hypericin);
- Medicinal products known to prolong the QTc interval (see Appendix 2 for a list of medications known to cause QTc prolongation);

- Strong inhibitors of CYP1A2, CYP2D6, and CYP3A4 listed in Appendix 3;
- Strong inducers of CYP3A4 listed in Appendix 3;
- Antimalarial agents, other than hydroxychloroquine (HCQ);
- Dapsone;
- Cyclosporin.

If a patient requires treatment with one or more of the listed prohibited medications, the patient may need to be taken off study treatment. Each individual case will be considered and if possible, the investigator should discuss with the Sponsor and Medical Monitor prior to initiating prohibited therapy.

8.7.3 Cautionary Therapy

The following medications should be used with caution and only when there is not another therapy option:

- Digoxin;
- Insulin or antidiabetic drugs;
- Beta-blockers;
- Monoamine oxidase inhibitors;
- Selective serotonin reuptake inhibitors;
- Medications with the possible risk for QTc prolongation.

In addition, antacids or kaolin should not be administered with hydroxychloroquine but may be administered 4 hours before or after hydroxychloroquine.

Should an investigator deem treatment with a listed cautionary medication necessary, monitoring should be increased as deemed appropriate by the treating investigator to ensure patient safety.

8.8 Duration of Therapy

Patients will receive combined treatment until treatment discontinuation criteria is met. Upon meeting treatment discontinuation criteria, patients will continue on the study in follow-up until study discontinuation criteria is met.

If the sponsor prematurely terminates the study, patients receiving clinical benefit from the study treatment will roll over to an expanded access protocol to ensure continued access to the study drug.

8.8.1 Criteria for the Discontinuation of Treatment

Discontinuation from the study drug does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in patient management is needed. Any new clinically relevant finding will be reported as an AE.

Patients may withdraw from treatment or the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Table 6, the following will result in treatment discontinuation:

- The patient or legally authorized representative withdraws consent from the study treatment and/or study procedures;
- Clinical deterioration that, in the opinion of the investigator, increases the risk to the patient;
- Confirmed disease progression based on radiographic progression per RECIST 1.1; except as permitted for radiation treatment of single site (e.g., bone/brain) metastasis as per Section 8.7.1. Also, in rare cases of radiographic progression, treatment may be continued for a patient who has met the criteria for radiographic progression but, in the Investigator's opinion, is receiving benefit, after discussion with MM;
- AEs or intercurrent illness that in the opinion of the investigator warrants the patient's withdrawal from study treatment;
- Significant non-compliance with the protocol schedule or treatment administration in the opinion of the investigator;
- Unacceptable toxicity;
- Pregnancy;
- Death.

8.8.2 Criteria for the Discontinuation of Study

Patients may withdraw from the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the

inability of the patient to comply with the protocol-required schedule of study visits or procedures. Patients must be withdrawn from the study for any of the following reasons:

- Completed study follow-up period;
- Patient or legally authorized representative requests to be fully withdrawn from the study;
- If, in the investigator's opinion, the continuation of the trial would be harmful to the patient's well-being;
- The patient is lost to follow-up;
- Patient non-compliance (at the discretion of the Principal Investigator);
- Screen failure;
- Death.

Patients will also be withdrawn at any time if the Investigator concludes that it would be in the patient's best interest for any reason. Protocol violations do not lead to patient withdrawal unless they constitute a significant risk to the patient's safety.

If the investigator withdraws the patient due to a reason not related to safety (i.e. patient compliance, ability to make appointments) and the patient has not reached the first assessment period (end of cycle 2) then the patient may be replaced.

The Investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the eCRF.

8.8.3 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to further treatment. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, became lost to follow-up for any reason, or if any of the following occurs:

- Discovery of patient ineligibility
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk.

Patients who withdraw consent for further participation in the study will not receive any further study drugs or further study observation.

If a patient withdraws prior to the first assessment period (end of cycle 2) for reasons not related to safety, then this patient may be replaced.

8.8.4 Lost to Follow-Up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

9 STUDY PROCEDURES

9.1 Screening

For screening procedures; see the SOA (Table 1) and Section 10. Screening activities may only begin after a patient has signed consent. Tests conducted for the standard of care monitoring and disease assessment may be used to prove eligibility if performed within the screening period. All screening activities must take place within 28 days before cycle 1 day 1 unless otherwise noted.

9.2 Treatment Period

Once a patient has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. See the SOA (Table 1) and Section 10 for treatment period procedures.

9.3 End of Treatment

Once treatment discontinuation criteria have been met, the End of Treatment (EOT) visit will occur. The EOT visit should occur when the decision to discontinue treatment is made. If this visit overlaps with a regularly scheduled visit, only the procedures listed in the calendar for the EOT visit will be performed. For EOT procedures see the SOA (Table 1) and Section 10.

9.4 Safety Follow-Up

Patients will return to the clinic or will be contacted for a safety follow-up assessment 60 ± 7 days after the last dose of study drug was taken; or earlier if subsequent therapy for advanced malignancy is initiated prior to 60 ± 7 days. Only information about AEs and SAEs will be collected at this visit.

9.5 Follow-Up

Patients that discontinue study treatment for any reason other than disease progression, must continue to have disease assessments every 8 weeks (± 7 days) until disease progression, the initiation of subsequent anti-cancer therapy, or death.

10 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

10.1 General Assessments

10.1.1 Patient Consent

Prior to the initiation of any study procedures, all potential patients or their legal representative must be fully informed of the risks and potential benefits of trial participation and demonstrate understanding. An informed consent document must be signed and dated by the patient or their legal representative indicating that they understand the risks and consent to participation and treatment on the study. The Principal Investigator or their appropriately trained and delegated study personnel conducting the informed consent discussion must also sign and date the document. A copy of the signed document should be provided to the patient.

Standard of care procedures performed prior to patient consent may contribute to the assessment of eligibility and/or screening procedures if performed within ±7 days prior to signing informed consent.

10.1.2 Medical History

The investigator or appropriately trained and delegated study personnel will collect medical history to the extent that supports the assessment of eligibility. Medical history will include any active conditions and any conditions deemed to be clinically significant by the treating investigator. The use of symptom terms should be discouraged; if possible, terms describing the principal condition or syndrome should be used. Special attention should be given to prior cancers (other than the one under study), prior anti-cancer therapies and/or surgeries, current smoking status, and smoking history. Additionally, female patients of childbearing potential should have the date of last menstrual cycle noted.

10.1.3 Prior and Concomitant Medications

All medications currently being used by a study participant, regularly or as needed, must be reviewed and documented by the investigator or qualified designee. Specific attention should be given to medications with a protocol-required washout as described in the exclusion criteria and any medication taken 28 days prior to cycle 1 day 1. The last dose of any prohibited medications requiring a washout as described in the exclusion criteria and Section 8.7.2 must be clearly documented in the patient's research chart.

Prior medications are considered those medications which are taken from signing of informed consent but stopped prior to the first day of study drug administration. Concomitant medications are any medications ongoing from signing informed consent through the first day of study drug or started after the first day of study drug.

During protocol therapy, any medications taken by the patient or used to treat an adverse event will be documented in the patient's research chart and the corresponding eCRF. If a new anti-cancer therapy is initiated during study follow-up, the new therapy should also be recorded in the patient's research chart and corresponding eCRF.

10.1.4 Tumor Mutation Testing

It is required that all patients have histological confirmation and documentation of the necessary MAPK mutation. To assess eligibility, cancer mutational status must be confirmed through patient medical records and recorded in the eCRF.

10.2 Safety Assessments

10.2.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of ECOG performance status (see Appendix 1), weight and height at the time points described in the SOA (Table 1). Vital signs include systolic/diastolic blood pressure (BP), heart rate (HR), respiration rate (RR), pulse oximetry, weight, and body temperature. Height will be measured at screening only. If necessary, to facilitate scheduling, the physical exam may occur one day prior to study treatment.

10.2.2 Adverse Events

AEs experienced during trial participation will be collected per the SOA (Table 1) and Section 11. Each study participant will be questioned about the occurrence of AEs in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study treatment, dose modification guidelines in Section 8.5 should be followed using the investigator's discretion.

10.2.3 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the SOA (Table 1) and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit (7 days for cycle 1 day 1). All safety laboratory analyses will be performed by the local laboratory for each study center. When applicable, all safety laboratory assessments must be reviewed by the treating investigator prior to study drug administration. When applicable, results from the pregnancy test must also be available for review prior to dosing.

Table 7: Laboratory Assessments

Laboratory Assessments	
Complete Blood Count (CBC) with Platelet Count and Differential	• White Blood Cell Count • Hematocrit/Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes

Chemistry	• Comprehensive Metabolic Panel
	  ○ Sodium
	  ○ Potassium
	  ○ Chloride
	  ○ Carbon Dioxide
	  ○ Alkaline Phosphatase
	  ○ Aspartate Aminotransferase
	  ○ Alanine Aminotransferase
	  ○ Urea Nitrogen
	  ○ Glucose
	  ○ Creatinine
	  ○ Calcium
	  ○ Protein
	  ○ Albumin
	  ○ Bilirubin
	• Uric Acid
	• Lactate Dehydrogenase
	• Creatine Kinase†
	• Inorganic Phosphorus

Coagulation	• PT (prothrombin time) • INR (international normalized ratio) • PTT (partial thromboplastin time)
Urinalysis	• Specific gravity • Protein • Glucose • Occult blood • Microscopic examination as clinically indicated
Pregnancy	• Beta-human chorionic gonadotropin (β-hCG) Qualitative Urine or Serum
Tumor Marker#	• Pancreatic adenocarcinoma only CA 19-9 • Colorectal carcinoma only CEA • Cholangiocarcinoma only CEA and CA 19-9

† After screening, creatine kinase should only be drawn if creatinine is elevated.
# Tumor markers are not required for patients with esophageal or stomach cancers.

10.2.4 12-Lead Electrocardiograms (ECG)

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. All patients will require single 12-lead ECG measurements according to the SOA (Table 1). The parameters to be recorded are HR, RR, QT, PR, and QRS. All ECGs should be conducted pre-dose and Fridericia's formula will be used for all QT correction calculations. Decisions for dose modifications for QTc prolongation will be made based on QTcF values.

If at any time after screening the QTcF > 500 ms, a triplicate ECG will be performed with tracings approximately one-minute apart. The mean QTcF from these ECGs should be used when following the dose modification guidelines.

10.2.5 Echocardiogram

A transthoracic echocardiogram will be used to assess left ventricular ejection fraction (LVEF) at screening and as clinically indicated during study treatment. Should a decline in LVEF occur, the dose modification guidelines should be followed.

10.2.6 Ophthalmologic Exam

A full ophthalmic examination (performed by an ophthalmologist or optometrist) will be performed at the time points described in the SOA (Table 1) and will include:

- Best-corrected distance visual acuity (BCVA), an automated threshold visual field (VF) of the central 10 degrees (with retesting if an abnormality is noted);
- Slit-lamp examination;
- Intraocular pressure;
- Dilated fundoscopy with attention to retinal abnormalities;
- Spectral-domain ocular coherence tomography (SD-OCT).

In patients of Asian descent, it is recommended that visual field testing be performed in the central 24 degrees instead of the central 10 degrees.

It is recommended that hydroxychloroquine be discontinued if ocular toxicity is suspected, and the patient should be closely observed given that retinal changes (and visual disturbances) may progress even after cessation of therapy.

All ophthalmology assessments must be conducted up to 7 days prior to the clinic visit to enable timely results review.

10.3 Efficacy Assessments

10.3.1 Disease Assessment

Disease assessments must include all known or suspected sites of disease; therefore, the decision for body areas to be scanned will depend on the extent of disease. The minimum recommended body areas to be scanned is chest, abdomen, and pelvis. Local treating investigators will evaluate disease assessments and define response per RECIST 1.1[38]. All treatment decisions will be based on the local treating investigator's assessment.

Disease assessments will be evaluated radiologically and conducted at baseline (within 28 days prior to the first dose of study treatment) and then every 8 weeks thereafter ≤ 7 days prior to the start of the following cycle (e.g., prior to cycle 3 day 1, cycle 5 day 1, cycle 7 day 1, etc.). If a response is observed (CR or PR), confirmation of response is required ≥ 4 weeks from the first documentation of response (note: a confirmation of response does not have to occur at the next scan. It can occur any time ≥ 4 weeks to 8 weeks). Disease assessments will continue until disease progression, the initiation of subsequent anti-cancer therapy, or death. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (e.g., symptomatic deterioration) or when clinically indicated. The schedule of tumor assessments should be fixed according to the calendar, starting with cycle 1 day 1, regardless of treatment delays or interruptions due to toxicity.

Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom Central Nervous System (CNS) involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Consistent imaging modality should be used for all disease assessments.

If a single site of metastasis (e.g., bone or brain) requires palliative radiation as described in Section 8.7.1, it will not necessarily be considered progressive disease and the patient will be allowed to continue study treatment after discussion with the Medical Monitor.

10.3.2 Correlative Studies

Correlative studies will focus on exploring the pharmacokinetics, pharmacodynamics, and biomarkers for response and/or resistance. To support these studies, de-identified biospecimens (blood and tissue) samples will be collected at the time points indicated on the SOA (Table 1). Any blood or tissue remaining after the completion of the correlative studies will be stored for use in future research. All correlative study samples need to be drawn when patients are at steady state.

10.3.2.1 Pharmacodynamics

To assess the extent of pharmacologic inhibition the study drugs produce, blood and tissue samples will be drawn in stage one only as indicated on the Schedule of Correlative Sample Collection (Table 2). Assays to investigate pharmacodynamic markers, including p62 and pRSK, will be deployed. These may include but are not limited to RPPA, Nanostring, and RNA-exome.

Refer to the lab manual for sample collection and processing instructions.

10.3.2.2 Pharmacokinetics

Pharmacokinetic studies will be conducted at the time points indicated in the Schedule of Correlative Sample Collection (Table 2). Patients enrolled in stage one will have blood drawn for the support of pharmacokinetic studies pre- and post-dose. However, patients enrolled in stage two will have blood drawn only pre-dose.

On the day of blood collection for the support of pharmacokinetic studies, patients will be instructed not to take their morning doses, but to wait to take them in the clinic. When taking the study drugs, a meal will be provided by the site. After pre-dose samples have been collected (≤ 1 hour prior to the morning dose), patients will be instructed to take their study drug, and post-dose blood will be drawn at 0.5 (±2 minutes), 1 (±3 minutes), 2 (±6 minutes), 4 (±12 minutes), 6 (±18 minutes), 8 (±24 minutes), and 12 hours (±36 minutes). Patients should not have cycle 1 day 15 PK blood draws if not at steady state. Steady state is reached after 5 days or 10 consecutive doses.

Refer to the lab manual for sample collection and processing instructions.

10.3.3 Tissue

Stage 1 patients will undergo a mandatory biopsy at the time points indicated in the Schedule of Correlative Sample Collection (Table 2). If a patient has undergone a biopsy ≤ 6 months prior to the planned cycle 1 day 1 and has not received any anti-cancer treatment since undergoing the biopsy, archival tissue from this biopsy may be used to fulfill screening tissue requirements. An optional biopsy will be offered to patients at the time of treatment discontinuation as noted in the SOA (Table 1). These tissues will be used to determine if observed responses are due to on-target effects of study treatment. Samples may also be used to explore possible biomarkers predictive of treatment efficacy. Tissue should be taken when patients are at steady state during treatment.

Testing may include, but is not limited to:

- DNA/RNA sequencing.
- Reverse-phase protein arrays.
- Immunohistochemistry.

- RNA-exome.

Instructions for collection and processing will be detailed in the lab manual.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the study (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening, need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AE information will be elicited by asking the patient a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”. AEs should be reported on the appropriate page of the eCRF.

11.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that occurs at any dose (including after the informed consent form (ICF) is signed and prior to dosing) that:

- Results in death
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or

convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period (see below). If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event should be reported using the term “disease progression” with a CTCAE severity of grade 5.

11.2 Adverse Event Reporting

The investigator and qualified designees are responsible for the detection, documentation, reporting, and follow-up of all AEs experienced by patients during trial participation. AEs and SAEs will be recorded from the signing of the consent until 60 days after the last dose of study drug or until initiation of subsequent anti-cancer therapy, whichever is earliest. The following information will be required for each adverse event:

- Event description, including severity as graded by the CTCAE v.5;
- The causality assessment to either study drug per the below definitions;
- Event duration;
- Any action taken to treat or manage the event;
- Event outcome.

11.2.1 Severity Assessment

The severity of AEs should be assessed by CTCAE v.5. If an event is not listed in CTCAE v.5, then the assessment of severity should follow the general guidelines listed in Table 8.

Table 8: Severity assessment

Grade	Severity Description
1	Mild event that generally does not require intervention.
2	Moderate event that may require intervention.
3	Severe event that requires intervention.
4	Life-threatening event that requires urgent intervention.
5	Death.

Events meeting grade 4 or 5 severity description should be reported promptly as SAEs unless otherwise indicated in Section 11.1.2.

11.2.2 Relationship to Study Drug

The Investigator will make a judgment regarding whether or not the AE was related to either study drug, as outlined below, and in accordance with FDA guidance of 2012.

Unrelated	The AE is unlikely to have been caused by study drug.
Possibly related	It is unclear whether the AE may have been caused by study drug.
Related	The AE is likely to have been caused by study drug.

11.2.3 Action Taken and Outcome

Start and stop dates will be required for all AEs and SAEs. The action taken in response to the event should also be recorded in the patient's research chart and corresponding eCRF. Event action terms include none, medication administered, non-drug therapy administered, surgery, hospitalization, or other with the option to specify. If a new medication is added the medication should also be added to the concomitant medications log.

All AEs should be followed until stabilization or resolution. Event outcomes may be classified as resolved, resolved with sequelae, ongoing, or death.

11.2.4 Reporting Serious Adverse Events

ALL SAEs must be entered into the eCRF within 24 hours of first knowledge of the event by study personnel. It is important that the investigator provide his/her assessment of relationship to study drug at the time of the initial report. Follow-up information must also be reported within 24 hours of first knowledge. Entry of an SAE (or updated SAE information) into the eCRF will trigger an automatic alert to the designated CRO Safety team. Timely notification of an event supersedes the requirement to have all information at the time of the initial report.

If the electronic data capture (EDC) system is **not available**, the Investigator must send a completed paper SAE Report Form to the CRO Safety team via email or fax as follows, within 24 hours. If no acknowledgement is received within one working day, the report should be re-submitted.

Safety Report Email Address: sae@cmedresearch.com

Safety Report Fax No.: 866.240.8830 (US) or +44 1403 330459 (international)

The SAE data must be entered into the eCRF as soon as it becomes available.

The following information must be reported on the eCRF SAE report form:

- Protocol number
- Site and/or Investigator number
- Patient number
- Demographic data
- Brief description of the event
- Onset date and time
- Resolution date and time, if the event resolved
- Current status, if event not yet resolved
- Any concomitant treatment and medication
- Investigator's assessment of whether the SAE was related to Investigative product or not
- Outcome of the event if available

The CRO Safety team will contact the site for clarification of data entered onto the eCRF, or to obtain missing information. In the event of questions regarding SAE reporting, the site may contact Cmed Drug Safety and Pharmacovigilance via email sae@cmedresearch.com.

Unexpected serious suspected adverse reactions are subject to expedited reporting to FDA. The CRO Safety team is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the FDA and to investigators participating in ongoing clinical studies with the study drug, according to 21 CFR 312.32 and the applicable guidance documents. All investigators participating in ongoing clinical studies with the study drug are responsible for prompt submission of these reports to their Institutional Review Board (IRB) or Ethics Committee (EC).

11.3 Special Situations

11.3.1 Pregnancy or Breastfeeding

Although pregnancy is not considered an adverse event, any exposure to the investigational products during pregnancy or breastfeeding must be reported to the sponsor promptly. Exposure may occur by a woman actively receiving study treatment or the partner of a male

patient actively receiving study treatment becoming pregnant. Any possible pregnancy or breastfeeding exposure during study treatment and up to 90 days after the last dose of study treatment or up to the start of subsequent anti-cancer therapy (whichever happens first) must be reported within 24 hours of awareness regardless of the occurrence of an SAE. Should a woman on study treatment become pregnant, she should immediately discontinue study treatment.

Women exposed to IP during pregnancy or while breastfeeding will be followed for pregnancy outcome and neonate health. Pregnancy outcomes may meet criteria as an SAE if ectopic pregnancy, spontaneous abortion, intra-uterine fetal demise, neonatal death, or congenital anomaly occurs. Congenital anomalies that occur in a live-born baby, a terminated fetus, an intra-uterine fetal demise, or a neonatal death should be reported as an SAE. Any neonatal deaths that occur up to 30 days after birth or breastfeeding exposure should be reported as an SAE. Further follow-up on birth outcomes and neonate health will be handled on a case-by-case base.

11.3.2 Hy's Law Cases

It is important to identify possible cases of Drug-Induced Liver Injury (DILI) early. Total bilirubin, Aspartate aminotransferase (AST), and alanine aminotransferase (ALT) should be regularly monitored for elevations indicative of liver damage. Patients who experience a transaminase elevation above three times the ULN should be monitored frequently to determine if the elevation is transient. Transient elevations are an indication of adaption, and these patients may be identified as "adaptors." However, should a transaminase elevation be followed by total bilirubin (TBili) increase, a DILI could be occurring. Any laboratory abnormalities meeting the following criteria should be reported into the EDC system within 24 hours of awareness:

- AST or ALT elevation > 3 x ULN; and
- Total bilirubin > 2 x ULN; and
- Absence of cholestasis; and
- No alternative explanation for the elevations.

Investigators should conduct reasonable investigations to rule out other possible etiologies. Investigators should take into consideration the patient's use of ethanol, acetaminophen, recreational drugs, herbal supplements, and medical history. A potential Hy's Law case will not be considered a confirmed case until all results and considerations have excluded alternative etiologies.

Patients who experience possible DILI should be managed per the Dose Modification Guidelines.

These events will not be collected by the CRO Safety Team unless they meet the criteria of an SAE.

11.3.3 Medication Error

The sponsor should be notified immediately (via an email from the clinical research associate) if a medication error occurs. Medication errors include:

- Patient dosing errors such as taking more medication than instructed;
- Medication uses outside of what is anticipated in the protocol;
- Medication errors that do not involve a trial patient.

Any medication errors resulting in an AE should be reported per AE/SAE reporting requirements.

Medication errors will not be collected by the CRO Safety Team unless they meet the criteria of an SAE.

11.4 Safety Oversight

An internal Safety Monitoring Committee (SMC) will be set up to review the safety of patients undergoing study treatment as the study progresses. The SMC will consist of a few Clinical Investigators, the Medical Monitor, and Sponsor representatives. The SMC will review any SAE that occurs during the study and will examine the safety of ulixertinib in combination with hydroxychloroquine, including toleration of the starting dose, dose interruptions, dose reductions, and toxicities that may occur in later cycles of treatment.

An assessment of dose tolerability will be determined by conducting an early safety review of the first 3 patients. The sponsor, CRO medical team, and the specific patients' Principal Investigators will do an extensive review of all AEs from the first 3 patients through a minimum of 1 cycle to ensure tolerability of the starting dose combination.

Before the expansion of any basket, the SMC will review the available safety and efficacy data of all patients enrolled in the specific basket. If necessary, the Medical Monitor can call ad-hoc meetings to review ongoing events and data.

Based on emerging safety data, the SMC may make study conduct recommendations including but not limited to: open a basket expansion cohort, discontinue enrollment to a basket, continue the study per protocol, protocol amendment, add safety procedures, perform additional analyses, hold enrollment or close the study.

12 STATISTICAL CONSIDERATIONS

12.1 General Considerations

The detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) covering all baskets. This section is a summary of the planned statistical analyses at the time of protocol development.

The safety and efficacy reviews to be conducted by the SMC will be addressed in the overall study SAP.

12.2 Sample Size Determination

Under Simon's optimal two-stage design[39] with a 5% significance level and 80% power, assuming a null hypothesis for ORR ≤ 20% versus the alternate hypothesis of ORR ≥ 40%, a total of 43 evaluable patients are required for the evaluation of the primary endpoint; 13 in stage 1 and an additional 30 in stage 2, for each basket.

In the first stage, if there are 3 or fewer patients achieving a response in the 13 evaluable patients, the study will be stopped for this basket. Otherwise, 30 additional patients will be accrued for a total of 43.

Then, if there are 12 or fewer responses in the 43 patients, the null hypothesis will not be rejected and any further investigation of the study drug in this basket will not be warranted. However, should at least 13 of the 43 evaluable patients achieve a response then the null hypothesis will be rejected, and it will be concluded that the study drug demonstrates activity for this basket to allow further investigation.

12.3 Population for Analyses

The full analysis set (FAS) will consist of all patients who received at least one dose of study drug. This analysis set will be used for all safety analyses.

The stage 1 analysis set (S1AS) will consist of the first 13 patients who have completed at least one cycle of therapy and who have received a minimum of 75% of prescribed study treatment during cycle 1. This analysis set will be used only for the purpose of the stage 1 efficacy analysis.

The evaluable analysis set (EAS) will consist of all patients who received at least one dose of study drug and have at least one post-treatment study evaluation or who have discontinued therapy prior to the first post-treatment study evaluation due to clinical progressive disease or drug-related AEs. This analysis set will be used for the evaluation of the primary efficacy endpoint, i.e., ORR.

The PK analysis set will consist of all patients who have received at least one dose of study drug and have at least one post-dose PK measurement. This analysis set will be used for PK analyses.

12.4 Data Analysis

Descriptive statistics for continuous variables will include the number of patients, mean, standard deviation, median, minimum, maximum; frequencies and percentages will be displayed for categorical data. No formal hypothesis testing will be performed.

Summary data will be provided by basket and overall.

Data will be analyzed using the SAS system software version 9.4 (or later).

12.4.1 Demographic and Baseline Characteristics

Demographics, medical history and other baseline data will be listed and summarized using descriptive statistics.

12.4.2 Prior and Concomitant Medications

The number and percentage of patients taking prior and concomitant medications will be summarized by therapeutic class and preferred term using descriptive statistics. All data will be recorded as follows:

- Prior medication: ended before the first day of study drug administration.
- Concomitant medication: ongoing at first day of study drug or started after first day of study drug.

12.4.3 Study Drugs

Exposure to ulixertinib and hydroxychloroquine will be summarized with descriptive statistics, including the duration of study drug exposure (in days), cumulative dose, dose intensity and relative dose intensity. The number of patients with dose reductions and interruptions will be presented by basket and overall, along with reasons for the dose modification. Exposure data will be listed.

12.5 Primary Endpoint Analysis

12.5.1 Safety and Tolerability

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 (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

AEs will be summarized based on the date of onset for the event. Summaries (number and percentage of patients) of treatment-emergent AEs will be provided by SOC and PT, by basket and overall.

Treatment-emergent adverse event (TEAE) is defined as any AE that emerges during treatment having been absent pre-treatment or worsens relative to the pre-treatment state.

The severity of the AEs will be graded according to the CTCAE v5.0.

The detailed information collected for each AE will be listed, including a description of the event, duration, severity, relatedness to study drugs, action taken, and clinical outcome.

AEs analysis will be conducted on the FAS.

12.5.2 Confirmed Overall Response Rate

Confirmed overall response rate will be calculated as the number of patients achieving a confirmed complete response or confirmed partial response (as per RECIST v1.1) divided by the total number of patients in the EAS. Patients without a confirmed response or a missing baseline/screening tumor assessment will be considered non-responders.

ORR will be reported along with a 95% exact binomial confidence interval (Clopper-Pearson method).

ORR analysis will be conducted on the EAS and replicated on the FAS.

12.6 Secondary Endpoints Analysis

12.6.1 Progression-Free Survival

Progression-free survival (PFS) will be defined as the time from study drug initiation until disease progression as per RECIST v1.1, or death from any cause. Patients with no event will be censored at the last available tumor assessment.

Kaplan-Meier estimates and curves, median PFS and its respective 95% confidence intervals (CIs) will be used to analyze PFS.

PFS analysis will be conducted on the EAS and replicated on the FAS.

12.7 Other Endpoints Analysis

12.7.1 Pharmacokinetics

For patients enrolled in stage 1 of each basket, PK concentrations of ulixertinib and hydroxychloroquine will be determined pre-dose and post-dose in plasma at cycle 1 day 15. Summary parameters such as AUC, C_{max}, C_{min}, $t_{1/2}$, t_{max} will be calculated.

PK parameters in plasma will be listed and summarized, by basket, using descriptive statistics (e.g., sample size, arithmetic and geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

For patients enrolled in stage 2 of each basket, PK parameters of ulixertinib will be measured on cycle 1 day 15. This will be a single timepoint collection prior to taking study drug on this day.

Pharmacokinetic values will be presented in by-patient listings.

PK analysis will be conducted on the PK analysis set.

12.7.2 Pharmacodynamics

Pharmacodynamic markers, including p62, will be explored and listed as appropriate. These may include but are not limited to RPPA, Nanostring, and RNA-exome.

PD analysis will be conducted on the FAS.

12.7.3 Laboratory Evaluations

The parameters associated with the clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be summarized with descriptive statistics by visit and for the change from baseline to each planned post-baseline visit, by basket and overall. Listings of all laboratory results and reference ranges will be provided.

Graded laboratory abnormalities will be defined using the grading scheme based on NCI CTCAE (v5.0) and summarized by basket and overall. Shift tables will also be produced for gradable parameters based on the baseline CTCAE grade and the maximum CTCAE grade. Only abnormal laboratory values deemed to be clinically significant by the investigator should be reported as AEs.

Analysis of laboratory evaluations will be conducted on the FAS.

12.7.4 Other Safety Evaluations

Changes in the patient's physical examination findings, vital sign parameters, and ECG will be summarized by basket and overall, and any abnormal values will be tabulated.

Listings of all data related to the patient's physical examination findings, vital signs and ECG will be provided.

Analysis of other safety evaluations will be conducted on the FAS.

13 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1 Regulatory, Ethical, and Study Oversight Considerations

13.1.1 Informed Consent Process

13.1.1.1 Consent And Other Informational Documents Provided to Patients

Consent forms describing in detail the study drug, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to performing any study-

related assessment which is not standard of care. Consent forms will be reviewed and approved by the appropriate IRB/EC prior to being given to potential participants.

13.1.1.2 Consent procedures and documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by an Institutional Review Board (IRB) and the patient will be asked to read and review the document. The investigator or designee will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patients for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed before the patient undergoes any study-specific procedures. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in the study.

13.1.2 Study Discontinuation and Closure

It is agreed that for reasonable cause, either the Investigator or the Sponsor may temporarily suspend or prematurely terminate this study or the Investigator's participation in this study, provided a written notice is submitted at a reasonable time in advance of intended suspension or termination. If discontinuation is by the investigator, notice is to be submitted to BioMed Valley Discoveries, Inc. If discontinuation is by the Sponsor, notice will be provided to each investigator. If the study is suspended or prematurely terminated, the Investigator will promptly inform the study patients, IRB, and the Sponsor will provide the reason(s) for the suspension or termination. Study patients will be contacted, as applicable, and be informed of changes to the study visit schedule.

If a severe local reaction or drug-related SAE occurs at any time during the study, the Safety Monitoring Committee will review the case immediately.

If one or more patients at any dose level develop any of the following AEs deemed to be possibly, probably or definitely related to ulixertinib by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors, the study will be immediately suspended and no additional ulixertinib doses will be administered pending review and discussion of all appropriate study data by the SMC:

- Death
- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress)

The study will not be restarted until all parties have agreed to the course of action to be taken and the Institutional Review Board/Ethics Committee (IRB/EC) (s) has/have been notified.

13.1.3 Confidentiality and Privacy

Patient confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Patient's data collected on eCRFs during the trial will be documented in a de-identified fashion and the patient will only be identified by the patient number, and/or by the patient's initials, if also required. The study data entry and study management systems used will be secured and password protected. If, as an exception, it is necessary for safety or regulatory reasons to identify the patient, all parties are bound to keep this information confidential.

The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the trial patients. All parties involved in the study will maintain strict confidentiality to assure that neither the person nor the family privacy of a patient participating in the trial is violated. Likewise, appropriate measures shall be taken to prevent access of non-authorized persons to the trial data.

13.1.4 Future Use of Stored Specimens and Data

With the patient's approval and as approved by local IRBs, de-identified biological samples will be stored for future analysis as warranted by the rapidly advancing understanding in this field. During the conduct of the study, an individual patient can choose to withdraw consent to have

biological specimens stored for future research. However, withdrawal of consent with regard to biological specimens' storage may not be possible after the study is completed.

Collected samples may be transferred for analysis to the Sponsor, or to other laboratories working for the Sponsor.

Biological samples will be stored for the time established by regulatory requirements or destroyed after the final clinical study report has been finalized if storage is not required. There might be a new request for these samples to be used for purposes related to the quality assurance of the laboratory tests described in this protocol, in which case they will be used for this purpose. This may include the assessment of the quality of current tests, the maintenance or improvement of these tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

If study results suggest that further investigations using stored biological samples are warranted, these tests might be carried out on an exploratory basis. In addition, biological samples may be used by the Sponsor or their research partners for further research that is not related to the disease or the product under study. This testing will be done on de-identified samples (meaning that any identification linking the patient to the sample is destroyed). Patients will be asked to sign an additional, separate consent form for this optional testing and refusal of consent will not affect their possibility of participating in the study.

13.1.5 Key Roles and Study Governance

13.1.5.1 Safety Oversight

An internal Safety Monitoring Committee (SMC) will be set up to review the safety of study treatment as the study progresses. The SMC will consist of a few Clinical Investigators, the Medical Monitor, and Sponsor representatives. The SMC will review any SAE that occurs during the study and will examine the safety of ulixertinib in combination with hydroxychloroquine, including toleration of the starting dose, dose interruptions, dose reductions, and toxicities that may occur in later cycles of treatment.

The safety review will be performed at regular intervals, at least semi-annually to access safety and efficacy data.

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 8.8.

13.1.5.2 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

A clinical monitoring plan will be developed by the Sponsor's CRO.

During the course of the study, a site monitor will conduct routine site visits to review protocol compliance, compare eCRF entries with individual patient's original source documents (accessed by the Investigator), assess product accountability and ensure the study is conducted according to applicable regulatory requirements. The review of the patient's original medical records shall be performed in a manner which ensures patient confidentiality is maintained.

The Investigator shall permit the site monitor to review study data as frequently as deemed necessary to ensure that data are recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator may not enroll patients into the study until such time that an initiation visit, or with the agreement of the Sponsor, attendance at the Investigator meeting, has been performed by the site monitor to conduct a detailed training of the protocol and eCRF.

13.1.5.3 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, data are generated, biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/sponsor's designee, and inspection by local and regulatory authorities. Key trial personnel must be available to assist monitors during visits.

13.1.5.4 Auditing Procedure

In addition to the routine monitoring procedures, the Sponsor or the regulatory authority can conduct an audit or an inspection (during the study or after its completion) to evaluate compliance with the protocol and the principles of GCP.

The investigator agrees that representatives of the Sponsor and regulatory authorities will have direct access, both during and after the course of this study, to audit and review all study-relevant medical records.

13.1.6 Data Handling and Record Keeping

13.1.6.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents. All information on CRFs (case report form) must be traceable to source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the CRFs, which will be documented as being the source data. All data requested on the eCRF must be entered and all missing data must be accounted for.

Clinical data and clinical laboratory data will be entered into a 21 CFR Part 11 compliant electronic data capture system. The data system includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.1.6.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

Study documents include:

- IRB/EC approvals for the study protocol and all amendments
- All source documents and laboratory records
- CRF copies (electronic copies on a CDROM)
- Patients' informed consent forms (with study number and title of trial)
- FDA form 1572
- Any other pertinent study document

13.1.7 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, ICH GCP, or study manual requirements. The non-compliance may be either on the part of the patient, Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing IRB per their policies. The Investigator is responsible for knowing and adhering to the review IRB requirements. Further details about the handling of protocol deviations will be included in the study manual.

13.1.8 Publication and Data Sharing Policy

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study may be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions, and the Sponsor.

All information provided to the investigator by BioMed Valley Discoveries, Inc., or their designee, will be kept strictly confidential. No disclosure shall be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than by BioMed Valley Discoveries, Inc., or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

13.1.9 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of person who has a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, person who have a perceived conflict of interest will be required to have such conflicts managed in such a way that is appropriate to their participation in the design and conduct of this trial.

13.1.10 Insurance

The Sponsor has established an insurance policy for the total anticipated duration of the study, covering the patients with respect to the risks involved in taking part in this study in accordance with this protocol. In the case of injury or disability deriving from participation in the study, patients are requested to inform the Investigator or his/her staff responsible for the study at the institution without delay.

14 REFERENCES

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Appendix 1: ECOG Performance Status[40]

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hour
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 2: List of QTc Prolonging Agents

Generic Name	Brand Names (Partial List)	Drug Class
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anti-cancer
Azithromycin	Zithromax, Zmax	Antibiotic
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
Fluconazole	Diflucan, Trican	Antifungal
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic
Ibutilide	Corvert	Antiarrhythmic
Levofloxacin	Levaquin, Tavanic	Antibiotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic

Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic
Oxaliplatin	Eloxatin	Anti-cancer
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Procainamide	Pronestyl, Procan	Antiarrhythmic
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Sevoflurane	Ultane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anti-cancer

Appendix 3: Prohibited Concomitant Medications

INHIBITORS		
CYP1A2	**CYP2D6**	**CYP3A**
ciprofloxacin	bupropion	ceritinib
fluvoxamine	fluoxetine	clarithromycin
	paroxetine	cobicistat
	quinidine	elvitegravir and ritonavir
	terbinafine	idelalisib
		indinavir and ritonavir
		itraconazole
INDUCERS		ketoconazole
CYP3A		lopinavir and ritonavir
apalutamide		nefazodone
carbamazepine		nelfinavir
enzalutamide		paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
ivosidenib[1]		posaconazole
lumacaftor and ivacaftor		ritonavir[3,4,5]
mitotane		saquinavir and ritonavir
phenytoin		tipranavir and ritonavir
rifampin		telithromycin
St. John's wort[2]		voriconazole

1: Based on PBPK simulation

2: The effect of St John's wort varies widely and is preparation dependent

3: Ritonavir is approved for use in combination with other anti-HIV or anti-HCV drugs. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of anti-HIV or anti-HCV combination regimens on CYP3A activities.

4: Moderate inducer of CYP1A2 with dosage of 800 mg/day ritonavir (not with other anti-HIV drugs). Effect on CYP1A2 at lower dosages of ritonavir is unknown.

5: Weak inducer of CYP2B6, CYP2C9, and CYP2C19. Classification is based on studies conducted with ritonavir itself (not with other anti-HIV drugs) at dosages of 100-200 mg/day, although larger effects have been reported in literature for high dosages of ritonavir.

Strong inhibitors: ≥ 5-fold increase in AUC

Strong inducers: ≥ 80% decrease in AUC

Table 1 (CYP Enzyme- and Transporter System-Based Clinical Substrates, Inhibitors, or Inducers) https://www.fda.gov/drugs/drug-interactions-labeling/healthcare-professionals-fdas-examples-drugs-interact-cyp-enzymes-and-transporter-systems, dated 06.05.2023; Accessed 08.30.2023