HUTCHMED

Clinical Study Protocol

AN OPEN-LABEL, MULTICENTER PHASE 1/2 STUDY OF SURUFATINIB IN COMBINATION WITH GEMCITABINE IN PEDIATRIC, ADOLESCENT, AND YOUNG ADULT PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

Short Title:	A Study of Surufatinib in Combination with Gemcitabine in Pediatric, Adolescent, and Young Adult Patients with Recurrent or Refractory Solid Tumors
Investigational Product(s):	Surufatinib (HMPL-012) Gemcitabine
Protocol Number:	2020-012-GLOB2
Clinical Phase:	Phase 1/2
Amendment:	3
Sponsor:	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
Regulatory Agency Identifier Number(s):	IND CCI [redacted] EudraCT 2021-003602-41
Issue Date:	24 January 2023

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this Clinical Study Protocol, Good Clinical Practice (GCP) as outlined by Internal Council for Harmonisation E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Re-consent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	An Open-Label, Multicenter Phase 1/2 Study of Surufatinib in Combination with Gemcitabine in Pediatric, Adolescent, and Young Adult Patients with Recurrent or Refractory Solid Tumors
Protocol Number	2020-012-GLOB2
Amendment	3
Version *(for sponsor's use only)*	1

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Name: [last name, first name] PPD	**Title:** PPD HUTCHMED International Corporation
Signature: *See appended signature page*	**Date:** [DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2020-012-GLOB2 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by International Council for Harmonisation (ICH) E6(R2)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent and updated consent in the event of new information or amendments, from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each patient's participation and all data required by the protocol

Name [Last name, first name]	**Title** [Title at institution]	**Institution** [Address]
Signature		**Date** [DD Month YYYY]

DOCUMENT HISTORY

Amendment	Issue Date
Original Protocol	02 Sep 2021
1	14 Oct 2021
2	03 Mar 2022

AMENDMENT SUMMARY

This Protocol 2020-012-GLOB2 Amendment 3 replaces Protocol 2020-012-GLOB2 Amendment 2. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary purpose of Amendment 3 is to provide notification that enrollment to study 2020-012-GLOB2 has been halted based upon the strategic evaluation of the clinical development of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who are deriving clinical benefit from treatment with surufatinib may continue to participate in the study as per the protocol. There is no planned interruption in the supply of surufatinib to clinical trial sites with active patients. In addition, as no patients have enrolled in study Part 2 (dose expansion) as of the end of enrollment date (16 December 2022), Part 2 is removed from the study design in this protocol Amendment 3. Part 1 (dose escalation) will continue as outlined in this protocol amendment. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Details of changes made in prior amendments are summarized in Appendix 10.

Section Number	Summary of Change	Rationale for Change
Section 1 – Synopsis Section 2.1.1 – Target Indication and Population Section 5.1 – Recruitment	Language was added to indicate that enrollment was halted as of 16 December 2022. Currently enrolled patients deriving clinical benefit from treatment may continue to participate in the study.	This new language confirms that the study halted enrollment on 16 December 2022. This language also confirms this change is not based on any patient safety or efficacy concerns, and to ensure patients deriving clinical benefit from study treatment may continue treatment.
Section 1– Synopsis Section 2 – Introduction Section 3 – Objectives and Endpoints Section 4 – Study Design Section 5 – Population Section 6 – Study Conduct Section 7 – Study Interventions Section 9 – Statistical Analysis	Remove all sub-sections and text presenting objectives, endpoints, disease cohorts, data collection/analysis and other information regarding study Part 2 Dose Expansion, including • Delete former Table 2 Schedule of Events for Part 2 • Delete former Table 4 Schedule of Events for Pharmacokinetic Evaluation for Part 2 • Delete former Table 8 Part 2 Objectives and Endpoints • Delete Figure 4 Dosing Schematic for Part 2 • Revise Figure 1 Study Schematic to remove Part 2: Simon's 2 Stage Design Combination Expansion. In addition, although Dose Escalation part of study is retained, references to Dose Escalation as "Part 1" are removed.	To remove Part 2 Dose Expansion from protocol.

Section Number	Summary of Change	Rationale for Change
Section 1– Synopsis Section 2.1.1 – Target Indication and Population	Synopsis "Condition/Disease:" Delete osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma. Synopsis "Health Measurement/Observation:" Delete efficacy time points for osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, non-rhabdomyosarcoma. Removed the following sub-sections: • 2.1.1.1 – Osteosarcoma • 2.1.1.2 – Ewing Sarcoma • 2.1.1.3 – Rhabdomyosarcoma • 2.1.1.4 – Non-Rhabdomyosarcoma.	To remove identification/analysis of/background for disease cohorts for study Part 2, which have been removed by this amendment.
Section 1– Synopsis Section 9.2.1 – Sample Size Rationale	Number of patients in study revised from "Up to 116 patients" to "Up to 36 patients".	To decrease planned number of patients since study Part 2 will not be performed.
Section 1– Synopsis Section 4.1 – Dose Escalation Section 4.3 – Design Rationale	Statement regarding number of patients in each of the 2 age range strata of pharmacokinetic (PK) expansion cohort changed from "…at least 6 patients…" to "…up to 6 patients…"	For clarification.
Section 1– Synopsis Section 3 – Objectives and Endpoints Section 4 – Study Design Section 6 – Study Conduct Section 7 – Study Interventions Section 9 – Statistical Analysis	Remove all sub-sections and text presenting information regarding objectives, endpoints, sample collection/analysis and data analysis for gemcitabine PK, including • Delete secondary objective "To document the PK exposure of gemcitabine when used in combination with Surufatinib" and corresponding endpoint "Observed plasma concentrations of gemcitabine". • Remove gemcitabine PK sample collection schedule from former Table 3 Schedule of Events for Pharmacokinetic Evaluation for Part 1 (revised presentation is Table 2 in this Amendment 3).	To remove gemcitabine pharmacokinetic (PK) sample collection and analysis and analysis of gemcitabine PK data.

Section Number	Summary of Change	Rationale for Change
Section 1– Synopsis Section 3 – Objectives and Endpoints Section 9.3.7 – Pharmacokinetics Analysis	The following secondary endpoint was deleted: "Observed plasma concentrations of surufatinib and estimated population PK and exposure parameters for Surufatinib." Delete paragraph describing population PK analysis.	To remove population PK analysis.
Section 1– Synopsis Section 3 – Objectives and Endpoints Section 6 – Study Conduct Section 9 – Statistical Analysis	Remove all sub-sections and text presenting information regarding objectives, endpoints, sample collection/analysis and data analysis for biomarkers, including • Delete exploratory objective "To correlate biomarkers to clinical response" and corresponding endpoint "Changes in circulating levels of, but not limited to, sVEGFR-2, VEGF, FGF, CSF-1, and IL-34". • Delete biomarker sampling row from Table 1 Schedule of Events. • Delete former Table 5 Schedule of Events for Biomarkers Evaluation: Part 1 and Part 2.	To remove biological sample collection for biomarkers and analysis of biomarker data.
Section 1– Synopsis Section 6.1.6 – Safety Follow-up	Delete long-term follow-up at 6 months and 1 year from the last dose of protocol therapy, including removing these time points and activity "Telephone follow-up" from Table 2 Schedule of Events.	To reduce required follow-up in the study to 30 days after end of treatment.
Section 9.3.1 – Disposition	Population for presentation of disposition data changed from "the safety analysis set" to "all enrolled patients."	For clarification.
9.3.4.1 – Objective Response Rate 9.3.4.2 – Duration of Response	The following text was added: Both confirmed and unconfirmed responses will be evaluated. To be assigned a status of confirmed PR or CR, the response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Add statement that duration of response will be summarized separately for both confirmed and unconfirmed responders.	For clarification.
9.3.5 – Safety Analysis	Added definition of treatment-emergent change in laboratory tests graded by NCI CTCAE version 5.0 or higher: defined as worsening of at least one grade from baseline.	For clarification
Section 2.1.4.3 – Toxicology	Provide results of definitive juvenile toxicity study in rats.	To provide updated information.

Section Number	Summary of Change	Rationale for Change
Section 4.1– Dose Escalation Section 5.4 – Exclusion Criteria Section 7.1.2 – Dosing and Administration Appendix 3 – Surufatinib Dosing Nomogram	Added statements and an exclusion criterion applicable for Spain sites only, indicating that no subjects with BSA less ≤0.6 or body weight ≤14 kg will be allowed to enroll in the study.	To add changes previously requested by Spain Health Authority and that were incorporated in prior Spanish Addendum 1 to 2020-012-GLOB2 Amendment 2.
Section 14 – References	Deleted publications no longer cited in protocol due to amendment.	To provide updated information.
Appendix 5 - Prohibited Concomitant Medications that Have a Known Risk of QT prolongation and/or Torsades de Pointes	List of prohibited concomitant medications with risk of QT prolongation and/or Torsades de Pointes has been updated.	To provide updated information.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Anteroposterior
aPTT	Activated partial thromboplastin time
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to time of last measurable concentration
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to time t
AUC_{0-tau}	Area under the plasma concentration-time curve over the dosing interval
AUC_{ss}	Area under the plasma concentration-time curve at steady state
BCRP	Breast cancer resistance protein
BML	Below measurable limit
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CL/F	Apparent total clearance from plasma after oral administration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form

Abbreviation	Definition
CRO	Contract research organization
CSF-1R	Colony stimulating factor 1 receptor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
epNET	Extra-pancreatic neuroendocrine tumor
EU	European Union
FDA	Food and Drug Administration
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FGFR-1	Fibroblast growth factor receptor 1
γ-GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GI	Gastrointestinal
hERG	Human ether-à-go-go-related gene
HR	Hazard ratio
HUVEC	Human umbilical vein endothelial cell
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IV	Intravenous

Abbreviation	Definition
KDR	Kinase insert domain receptor
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTKI	Multi-tyrosine kinase inhibitors
MUGA	Multigated acquisition
NCI	National Cancer Institute
NE	Not evaluable
NET	Neuroendocrine tumors
NOAEL	No-Observed-Adverse-Effect Level
NR	Not reached
NRSTS	Non-rhabdomyosarcoma soft tissue sarcoma
ORR	Objective response rate
P/C	Protein/creatinine
PD	Pharmacodynamic(s)
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
P-gp	P-glycoprotein
p-KDR	Kinase insert domain receptor phosphorylation
PK	Pharmacokinetic(s)
pNET	Pancreatic neuroendocrine tumor
PR	Partial response
PT	Preferred term
PT	Prothrombin time
QD	Once daily
QTc	Corrected QT interval(s)
QTcF	Corrected QT interval by Fridericia
RECIST	Response Evaluation Criteria in Solid Tumors
RMS	Rhabdomyosarcoma
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable disease
SOC	System Organ Class
SOE	Schedule of events
SRC	Safety Review Committee
SSRI	Selective serotonin reuptake inhibitor
STS	Soft tissue sarcoma
$T_{1/2}$	Half-life
T4	Free thyroxine
TAM	Tumor associated macrophage
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TGI	Tumor growth inhibition
TKI	Tyrosine kinase inhibitor
T_{max}	Time to reach the maximum plasma concentration
TSH	Thyroid stimulating hormone
TTR	Time to response
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1 SYNOPSIS

Title	An Open-Label, Multicenter Phase 1/2 Study of Surufatinib in Combination with Gemcitabine in Pediatric, Adolescent, and Young Adult Patients with Recurrent or Refractory Solid Tumors
Short Title	A Study of Surufatinib in Combination with Gemcitabine in Pediatric, Adolescent, and Young Adult Patients with Recurrent or Refractory Solid Tumors
Acronym	Not applicable
Phase	Phase 1/2
Study Status as of Protocol Amendment 3	As of 16 December 2022, enrollment to study 2020-012-GLOB2 was halted based upon the strategic evaluation of the clinical development of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who are deriving clinical benefit from treatment with surufatinib may continue to participate in the study as per the protocol. There is no planned interruption in the supply of surufatinib to clinical trial sites with active patients. In addition, as no patients have enrolled in study Part 2 (dose expansion) as of the end of enrollment date, Part 2 is removed from the study design in this protocol Amendment 3. Part 1 (dose escalation) will continue as outlined in this protocol amendment.
Rationale	Pediatric patients with recurrent or refractory solid tumors continue to experience dismal outcomes despite advances through much of pediatric oncology. There is an unmet need for better treatments for pediatric patients with solid tumors. This study will be performed on pediatric patients with recurrent or refractory solid tumors who have no known curative therapy. Although surufatinib monotherapy has shown clinical activity in adults with neuroendocrine tumors and in select adult cancer models, this study proposes that adding a chemotherapy agent in combination with surufatinib will provide added benefit for pediatric patients with refractory/recurrent solid tumors. Many current pediatric early phase studies combine an investigational agent with an irinotecan/temozolomide backbone both for anti-tumor effect and because of the tolerability and non-overlapping toxicities of the irinotecan/temozolomide backbone. However, irinotecan and temozolomide have shown limited effect in patients with osteosarcoma, a population of patients who may benefit most from a selective colony stimulating factor 1 receptor (CSF-1R) inhibitor such as surufatinib. Gemcitabine is a pyrimidine antimetabolite that inhibits tumor growth by disrupting deoxyribonucleic acid replication. Gemcitabine has been used as salvage chemotherapy alone and in combination in pediatric patients with relapsed/refractory sarcomas, particularly in patients with osteosarcoma but also in those with Ewing sarcoma or rhabdomyosarcoma (RMS). In phase 1 testing of gemcitabine in pediatric patients, no maximum tolerated dose (MTD) was reached, with only 1 in 6 patients experiencing Grade 4 myelosuppression when treated with 2100 mg/m^2 of gemcitabine once weekly for 2 weeks in 28-day cycles.
Target Population	Pediatric, adolescent and young adult patients (age range ≥2 and <18 years of age for United States [US] sites, from birth to <18 years of age for European Union/United Kingdom [EU/UK] sites) with any recurrent or refractory solid tumors or lymphoma (not central nervous system) who have a known or expected dysfunction of vascular endothelial growth factor receptor-1, -2, and -3; fibroblast growth factor receptor 1, or CSF-1R pathways. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

Intervention	Surufatinib and gemcitabine will be administered as outlined in study summary.
Description of Sites	Approximately 30 study sites (~15 in the US, ~15 in EU/UK).

Objectives and Endpoints

Objective	**Corresponding Endpoints**
Primary	
• To determine MTD and/or recommended phase 2 Dose (RP2D) of surufatinib, and to evaluate the safety and tolerability of surufatinib in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma	• The incidence of dose limiting toxicities in each dose level • Safety, as assessed by: o The frequency and severity of adverse events (AEs) o Physical examination findings o Vital signs o Laboratory test results o 12-lead electrocardiogram (ECG)
Secondary	
• To characterize the pharmacokinetics (PK) of surufatinib as a monotherapy and in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma	• Pharmacokinetic parameters for the dose escalation and PK expansion cohorts: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC), minimum plasma concentration (C_{min}), effective half-life ($t_{½}$), apparent total clearance from plasma after oral administration (CL/F), and accumulation ratio
• To evaluate the anti-tumor activity of surufatinib in combination with gemcitabine in pediatric patients with recurrent/refractory solid tumors or lymphoma	• Efficacy endpoints evaluated per RECIST version 1.1: o Objective response rate (ORR) o Disease control rate (DCR) o Time to response (TTR) o Duration of response (DoR) o Progression-free survival (PFS)
• Acceptability and palatability of surufatinib oral suspension	• The taste and palatability survey

Brief Summary:

The purpose of this study is to evaluate the safety and tolerability of surufatinib, thereby identifying the MTD and/or RP2D of surufatinib administered in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma.

The study will evaluate tolerability and safety of surufatinib administered in combination with gemcitabine, and provide confirmation of the recommended clinical dose of surufatinib in pediatric patients with recurrent or refractory solid tumors

The study will enroll 2 to 6 patients per dose level cohort (up to 4 cohorts) with recurrent or refractory solid tumors. During cycle 1, surufatinib will be administered, orally, once daily (QD), as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine intravenously on days 15 and 22 (cycle 1 duration=35 days) and days 1 and 8 of all subsequent cycles (cycle duration=21 days).

Assessment based on dose limiting toxicity (DLT) criteria will be performed in the first 35-day cycle (DLT Evaluation Period). This study will utilize a rolling 6 design, with 3 dose escalation levels and 1 de-escalation level, if needed.

At the MTD/RP2D, a PK expansion cohort will be planned to ensure that up to 6 patients <12 years of age and 6 patients ≥12 and <18 years of age have been evaluated at the MTD/RP2D.

Patients can remain on treatment until completing cycle 17, or until progressive disease, unacceptable toxicity, or death; whichever comes first. Follow-up on this study is required at 30 days after the last dose of protocol therapy.	
Condition/Disease	Recurrent or refractory solid tumors or lymphoma
Study Duration	Estimated 36 months
Treatment Duration	Approximately 12 months (including 24 months enrollment). Treatment duration is anticipated to be 6 to 12 months for individual patients.
Health Measurement/Observation	DLTs Safety (AEs, physical examination, vital signs, laboratory test results, and ECG) Efficacy (DCR, ORR) Acceptability/palatability (the taste and palatability survey)
Visit Frequency	Screening will occur within 28 days of study day 1. Cycle 1: days 1, 8, 15, 22, and 29 Cycle 2 and onward: day 1, 8, and 15 Safety follow-up: 30 days after last dose
Number of Patients	Up to 36 patients in dose escalation cohorts.
Intervention Groups and Duration	Surufatinib starting dose will be 120 mg/m^2 daily. The first study cycle will be 35 days. During cycle 1, surufatinib will be administered, orally, QD, as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine (1000 mg/m^2 weekly × 2 doses) intravenously on days 15 and 22. Surufatinib dose can be decreased by 1 dose level or increased up to 2 dose levels from starting dose based on tolerability. Gemcitabine will not be escalated, and will be given on days 1 and 8 of all subsequent cycles. After cycle 1, cycle duration is 21 days.
Safety Review Committee	Yes

1.1 Study Schematic for 2020-012-GLOB2

The study schematic is presented in Figure 1.

Figure 1 Study Schematic

Part 1: Rolling six design with 4 dose levels
Combination Dose Finding
Patients: All recurrent/refractory solid tumors, including lymphoma

Dose Level	Cycle 1 (Cycle duration 35 days)	
	Surufatinib (mg/m^2)	Gemcitabine Days 15 and 22(mg/m^2)
-1	90	1000
1	120	1000
2	160	1000
3	200	1000

Determine RP2D of Surufatinib and Gemcitabine in combination

PK Expansion Cohort at RP2D (12 patients)

PK=pharmacokinetic(s); RP2D=recommended phase 2 dose.

1.2 Schedule of Events

The schedule of events (SOE) is presented in Table 1. The SOE for pharmacokinetic (PK) evaluation appears in Table 2. For detailed description of each event please reference Section 6.1.

Table 1 Schedule of Events

Activity	Screening		Treatment Phase								Safety Follow-up
			Cycle 1 (35 days)					Subsequent Cycles (21 days per cycle)[1]			
	Day -28 to Day -2	Day -14 to Day -1	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)	Day 29 (±1d)	Day 1 (±3d)	Day 8 (±3d)	Day 15 (±3d)	30 days after last dose (±7d)
Informed consent	X										
Eligibility criteria review		X									
Demographics	X										
Medical history	X										
Medication review	X		X					X			
Pregnancy test[2]		X	X[3]					X			X
Complete physical exam[4]		X									
Limited physical exam[4]			X	X	X	X	X	X	X	X	X
Performance score (Lansky or Karnofsky, or ECOG)		X	X	X	X	X	X	X			X
Vital signs[5]		X	X	X	X	X	X	X	X	X	X
BP[6]		X	X	X	X	X	X	X	X	X	X
Height[7]		X						X			
Weight[7]		X						X			
Triplicate 12-lead ECG[8]		X						Day 1 of every even cycle (ie, cycles 2, 4, 6, 8, etc.)			X
Echocardiogram or MUGA	X										X
Chemistry panel[9]		X	X[3]	X	X	X	X	X			X
CBC with differential[10]		X	X[3]	X	X	X	X	X	X	X	X

Table 1 Schedule of Events

Activity	Screening		Treatment Phase								Safety Follow-up
			Cycle 1 (35 days)					Subsequent Cycles (21 days per cycle)[1]			
	Day -28 to Day -2	Day -14 to Day -1	Day 1	Day 8 (±1d)	Day 15 (±1d)	Day 22 (±1d)	Day 29 (±1d)	Day 1 (±3d)	Day 8 (±3d)	Day 15 (±3d)	30 days after last dose (±7d)
Coagulation assay (aPTT, PT/INR)		X	X[3]					X			X
TSH, T4		X						X			
Urinalysis[11]		X	X[3]	X	X	X	X	X			X
Tumor assessments	X		Day 1 of cycles 3, 5, 7, 9, 12, 15, end of cycle 17, and after every 3 cycles thereafter.								
Bone marrow biopsies[12]		X	Day 1 of cycles 3, 5, 7, 9, 12 and 15, and end of cycle 17[13]								
Knee X-ray	X		Every 6 months and end of treatment[14]								
Pharmacokinetics			PK schedule per Table 2								
AE reporting	Collected throughout time on study started at signing of informed consent										
Patient diary			X	X	X	X	X	X	X	X	
Taste and palatability survey[15]			X	X							
Surufatinib dosing			Dosed daily at a dose according to the assigned dose level								
Gemcitabine dosing					X	X		X	X		

AE=adverse event; AP=anteroposterior; aPTT=activated partial thromboplastin time; BP=blood pressure; CBC=complete blood count; d=day; DLT=dose limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; INR=International normalized ratio; MRI=magnetic resonance imaging; MUGA=multigated acquisition; PK=pharmacokinetics; PT=prothrombin time; QTcF=Corrected QT interval by Fridericia; T4=free thyroxine; TSH=thyroid stimulating hormone.

1. Assessments may be obtained within 3 days prior to the start of subsequent cycles unless otherwise indicated.
2. All female patients of childbearing potential must complete a serum pregnancy test at screening and at the safety follow-up visit, and a serum or urine pregnancy test on day 1 of every cycle starting at cycle 2. Additional procedural details for pregnancy testing are available in Section 6.1.2.8.
3. Laboratory tests need not be repeated at cycle 1 day 1 if therapy starts within 72 hours of obtaining laboratory test to assess eligibility.
4. Complete physical examination refers to the examination of all body systems. Limited physical examination includes vital signs, any change from baseline abnormalities, any new abnormalities, height, weight, and evaluation of patient-reported symptoms.
5. Procedural details for vital signs are available in Section 6.1.2.2.
6. Triplicate BP is required at baseline and at subsequent clinic visits if baseline BP is abnormal. Wait for 1 to 3 minutes between BP readings.

7. Assessments can be done up to 7 days before scheduled visit.
8. ECGs should be performed in triplicate at screening or if single read has a QTcF of ≥480 ms, and whenever feasible. Additional procedural details are provided in Section 6.1.2.9.
9. Procedural details for blood chemistry are available in Section 6.1.2.4.
10. If patient develops Grade 4 neutropenia, then CBC/differential count should be checked twice weekly (every 3 to 4 days) until recovery to Grade 3 or until meeting the criteria for DLT.
11. If urinalysis shows ≥ trace protein, then obtain urine P/C (protein/creatinine). A 24-hour urine sample for quantitative protein should be collected, if possible, for patients with ≥2+ proteinuria.
12. If bone marrow disease clinically suspected.
13. Only required if bone marrow biopsy at start of therapy was positive and until resolution.
14. The X-ray of the right or left knee (tibial AP and lateral views) will be obtained for all patients at screening. The follow-up X-rays (of the same knee obtained at screening) only need to be repeated in patients with open growth plates at study entry. If abnormalities are detected on routine X-rays, an MRI scan of both knees should be performed.
15. Parents of pediatric patients taking surufatinib oral suspension should complete the taste and palatability survey on day 1 and day 8 of cycle 1.

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Table 2 Schedule of Events for Pharmacokinetic Evaluation

Study Day	Surufatinib Administration and PK Samples		
	Time Relative to Surufatinib Dosing	Surufatinib Administration[1]	Surufatinib PK Samples[2,3]
C1D1	Predose[4]	-	X
	0 h	X	-
	1 h	-	X
	2 h	-	X
	3 h	-	X
	4 h	-	X
	8 h	-	X
C1D2	Predose[4]	-	X
C1D8	Predose[4]	-	X
	0 h	X	-
C1D15	Predose[4]	-	X
	0 h	X	-
	-	-	-
	-	-	-
	1 h	-	X
	2 h	-	X
	3 h	-	X
	4 h	-	X
	8 h	-	X
C1D16	Predose[4]	-	X[5]
C1D22	Predose[4]	-	X
	0 h	X	-
	-	-	-
C1D29	Predose[4]	-	X
	0 h	X	-
Day 1 of sub-sequent cycles[6]	Predose[4]	-	X or X
	0 h	X	
	≥3 h	-	

CxDx=cycle x day x; eCRF=electronic case report form; h=hour(s); ; PK=pharmacokinetic(s).

1. Study treatment must be taken at the investigative site under the supervision of the Investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered at the site and the dose prior to the visit must be recorded.
2. The date and time of the PK samples must be recorded in the eCRF.
3. Allowable sampling time deviation windows are ±5 minutes for 1 hour, ±10 minutes for 2 hours, 15 minutes for 3 and 4 hours, and 30 minutes for 8 hours.
4. Predose PK should be performed within 60 minutes before study treatment administration.
5. The C1D16 predose PK may be omitted only if a predose PK sample on C1D15 is collected.
6. On day 1 of subsequent cycles, 1 PK sample is to be obtained either at predose or at least 3 hours postdose.

2 INTRODUCTION

2.1 Background

Relapsed and refractory solid tumors for which there are few effective treatment options are a significant source of morbidity and mortality in pediatric oncology. Surufatinib is a novel small molecule kinase inhibitor that modulates the tumor microenvironment by inhibiting tumor-associated macrophages (TAMs) while also targeting tumor angiogenesis. It selectively inhibits colony stimulating factor 1 receptor (CSF-1R), vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, and fibroblast growth factor receptor 1 (FGFR-1) (Xu 2019). In human tumor xenograft models of cancer in adults (gastric cell carcinoma and renal cell carcinoma), it has potent anti-angiogenesis activity and improved kinase selectivity compared to earlier generations of small molecule tyrosine kinase inhibitors (TKIs) (Surufatinib Investigator's Brochure [IB]).

Tumor associated macrophages in the tumor microenvironment are well described cells that affect the ability of many solid tumors to evade the host immune system, and high levels of TAMs have been associated with poor prognoses in a variety of solid tumors (Lewis 2006). CSF-1R plays a critical role in signal transduction leading to the differentiation and persistence of macrophages and is a known mediator that promotes TAMs within the microenvironment. CSF-1R modulates differentiation, proliferation, and survival via PI3K or the RAF/MEK/ERK pathways. Regulation of cell adhesion and migration is modulated by the binding of CSF-1 to CSF-1R leading to phosphorylation of Focal Adhesion Kinase, which activates signaling, leading to cytoskeleton remodeling, adhesion, and migration. The downstream effects of CSF-1/CSF-1R blockade produce an environment of decreased immune suppression and increased interferon response, impeding tumor growth (Osipov 2019). CSF-1R is expressed on a wide range of solid tumor cells, including osteosarcoma, and its inhibition suppresses osteosarcoma tumor cell line proliferation and growth in mice (Wen 2017). CSF-1R inhibition sensitizes tumor cells to cytotoxic chemotherapy including cisplatin and trabectedin.

CSF-1R is encoded by the c-fms proto-oncogene and is included as a relevant target in the National Cancer Institute (NCI)/Food and Drug Administration (FDA) Molecular Target List for the RACE for Children Act. CSF-1R has 2 known ligands, CSF-1 and interleukin 34 (IL-34). CSF-1 is produced by fibroblasts, endothelial cells, monocytes, macrophages, osteoblasts, microglia, keratinocytes, bone marrow stroma, NK cells, B cells, and T cells. Physiologic roles of CSF-1 include survival, proliferation, differentiation, and motility of cells in the monocyte lineage, as well a bone remodeling by osteoclasts (Rovida 2015, Achkova 2016). CSF-1R overexpression promotes proliferation, migration, and invasion of the nasopharyngeal carcinoma cell line 6-10B (Chen 2018). In osteosarcoma cell lines, overexpression of CSF-1R enhances cell proliferation and accelerates cell growth, migration, and invasion. Silencing of CSF-1R by ribonucleic acid (RNA) interference suppresses proliferation and osteosarcoma tumor growth in mice (Wen 2017). Xenograft mouse models using orthotopic osteosarcoma cell line and subcutaneous patient-derived xenografts, pexidartinib (kinase inhibitor targeting CSF-1R) treatment significantly inhibited local osteosarcoma tumor growth and lessened metastatic burden (Smeester 2020). Additionally, in murine neuroblastoma models, CSF-1R inhibition in combination with cyclophosphamide and topotecan inhibited tumor growth and improved mouse survival (Webb 2018).

Small molecule and monoclonal antibody CSF-1R inhibitors are in clinical development both as monotherapy and in combination therapy (chemotherapy and/or immunotherapy) in adults with solid tumors and have demonstrated good tolerability (Cannarile 2017). Pexidartinib is approved for the treatment of tenovial giant cell tumor in the United States (US) and has also demonstrated clinical activity (response rate 5%) as a monotherapy in a phase 2 study for relapsed or refractory Hodgkin lymphoma (HL). Although the efficacy of single agent PLX3397 in this study population was modest, the manageable safety profile and evidence of target inhibition may warrant further testing in combination therapy studies (Moskowitz 2012). JNJ-40346527, a selective inhibitor of CSF-1R tyrosine kinase, has shown clinical activity (1 patient with CR, 10 patients with stable disease [SD] of total 21 patients) in the phase 1 study for relapsed or refractory classical HL (von Treskow 2013). Lastly, in a phase 1 study of AMG 820, an investigational fully human CSF-1R antibody in adult patients with relapsed or refractory advanced solid tumors, AMG 820 was tolerated with manageable toxicities and clinical activity was observed (objective response rate [ORR] 4%; clinical benefit rate [CBR] 24% in 25 patients) (Papadopoulos 2017).

VEGF-mediated signaling plays a critical role in tumor growth by promoting angiogenesis, and high levels of VEGF expression are seen across a wide range of pediatric tumors, including neuroblastoma, osteosarcoma, Ewing sarcoma, Wilms tumor, and rhabdomyosarcoma (RMS), and are associated with recurrence and poorer prognoses (Ghanem 2003, Eggert 2000, Gee 2005). Additionally, solid tumors depend on vascular supply, and the inhibition of tyrosine kinases that promote tumor angiogenesis, including VEGFRs and FGFR-1, is a well described potential therapeutic target in patients in wide ranging solid malignancies. Demonstration of clinical activity of multi-tyrosine kinase inhibitors (MTKI) such as regorafenib and cabozantinib have re-vitalized interest in MTKI, including those with VEGFR inhibition in solid tumors in children.

2.1.1 Target Indication and Population

As of 16 December 2022, enrollment to study 2020-012-GLOB2 was halted based upon the strategic evaluation of the clinical development of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who are deriving clinical benefit from treatment with surufatinib may continue to participate in the study as per the protocol. There is no planned interruption in the supply of surufatinib to clinical trial sites with active patients. In addition, as no patients have enrolled in study Part 2 (dose expansion) as of the end of enrollment date, Part 2 is removed from the study design in this protocol Amendment 3. Part 1 (dose escalation) will continue as outlined in this protocol amendment.

Although outcomes in pediatric cancer have improved significantly in recent years, the prognosis is still poor for pediatric patients with recurrent, refractory, or metastatic disease. There remains a need for more effective therapies for these patients. The study will include pediatric, adolescent, and young adult patients ≥2 and <18 years of age (for US sites) and from birth to <18 years of age (for European Union/United Kingdom [EU/UK] sites) who have recurrent or refractory solid tumors or lymphoma with no known curative therapy.

2.1.2 Description of Gemcitabine

Gemcitabine inhibits cell cycles progression and acts as a deoxyribonucleic acid (DNA) synthesis inhibitor. Gemcitabine PK is linear and is described by a 2-compartment model. Gemcitabine half-life ($T_{1/2}$) for short infusions (<70 minutes) ranged from 42 to 94 minutes, and the value for

long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution (V_d) with longer infusions. The inactive metabolite of gemcitabine is excreted in the urine with 92% to 98% of the gemcitabine dose excreted in the urine within 1 week of administration.

2.1.3 Description of Surufatinib

Surufatinib is a novel TKI that inhibits VEGFR 1, 2, and 3, as well as FGFR-1, which results in inhibition of angiogenesis. In addition, surufatinib inhibits signaling via CSF-1R, which is thought to down-regulate TAMs, thus promoting anti-tumor immunity.

2.1.3.1 Justification for Dosing Strategy

The recommended phase 2 dose (RP2D) for surufatinib is 300 mg/day in adults. Surufatinib has not been studied in pediatric patients. This study proposes to conduct a phase 1/2 study of surufatinib in combination with gemcitabine in pediatric patients with relapsed or refractory solid tumors or lymphoma with no known curative therapy. This dose finding study will use a rolling 6 design (Simon 1989).

In adults receiving 200 to 350 mg per day of surufatinib, the $T_{1/2}$ was 19.5 hours, and similar exposure accumulation was reached on days 14 and 28, indicating that a steady state was achieved on day 14 with the mean accumulation index of 1.8- to 2.7-fold. The starting dose of 120 mg/m^2 once daily (QD) surufatinib in pediatric patients will be 70% of the adult RP2D (300 mg for a 70 kg adult=175 mg/m^2) and will be dosed based on body surface area (BSA). Gemcitabine will be administered intravenously at a dose of 1000 mg/m^2 weekly × 2 doses, which has efficacy in pediatric sarcomas. Cycle 1 will aim to establish tolerability and safety and to obtain PK of surufatinib as a single agent and in combination with gemcitabine.

The proposed starting dose of 120 mg/m^2 surufatinib in pediatric patients is further supported by a model-based approach. Based on population PK model analysis, a 120 mg/m^2 dose is proposed for pediatric patients aged 2 to 5 years old and a 140 to 160 mg/m^2 dose is proposed for pediatric patients aged 5 to 18 years old. These proposed dosing regimens are predicted to result in surufatinib area under the plasma concentration-time curve at steady state (AUC_{ss}) to fall within the target therapeutic exposure, derived from the 10th to 90th percentile of surufatinib AUC_{ss} after 300 mg QD dosing that demonstrated efficacy in patients with neuroendocrine tumors (NETs), in more than 98% of the pediatric patients.

2.1.4 Supportive Nonclinical Data

2.1.4.1 Pharmacology

Surufatinib (HMPL-012, also previously known as sulfatinib) is a small molecule oral kinase inhibitor with selective and potent inhibition of CSF-1R (half maximal inhibitory concentration [IC_{50}] 4nM), VEGFR 1 (IC_{50} 2nM), VEGFR 2 (IC_{50} 24nM), VEGFR 3 (IC_{50} 1nM), and FGFR-1 (IC_{50} 15nM), with significantly weaker effect on other kinases such as PDGFR, c-KIT, and YES.

Consistent with its biochemical activity on kinase insert domain receptor (KDR) kinase inhibition, surufatinib demonstrated strong inhibitory activity on VEGF-stimulated phosphorylation of KDR in the HEK293-KDR engineered cell line, with an IC_{50} of 2 nM. In addition, the activation of KDR downstream signaling cascade pathways, including those of PI3K/AKT,

RAS/RAF/MEK/ERK, and p38 were also inhibited in a dose-dependent manner. Furthermore, in functional assays using human umbilical vein endothelial cells (HUVECs), surufatinib inhibited VEGF-dependent cell proliferation, with an IC_{50} of 16 nM, and inhibited 75% of HUVEC tube formation with at 0.3 μM. In the rat aortic ring model, surufatinib inhibited vessel outgrowths of rat aortic rings in a dose-dependent manner with an IC_{50} of 192 nM.

Surufatinib has been evaluated for cytotoxicity in 11 human tumor cell lines and 3 normal human cell lines. Surufatinib showed a weak effect on cell survival with IC_{50}≥5 μM, which was about 300-fold less potent than the IC_{50} of surufatinib in a VEGF-dependent anti-proliferation assay in HUVEC (16 nM), consistent with its good kinase selectivity.

The inhibitory effect of surufatinib on the phosphorylation of KDR, angiogenesis, and tumor growth have been evaluated in vivo. Upon stimulation with VEGF (intravenous [IV], 0.5 μg/mouse), KDR phosphorylation (p-KDR) in the mouse lung tissue was significantly induced. Surufatinib administered orally completely inhibited VEGF-stimulated KDR phosphorylation for 4 hours at 20 and 40 mg/kg and for 8 hours at 80 mg/kg, which suggest dose-dependent inhibition. In this experiment, the drug exposure was determined. For instance, at 4 hours after oral administration of 20 mg/kg of surufatinib, the drug concentration in plasma reached 181 ng/mL (area under the plasma concentration-time curve [AUC] for 20 mg/kg was 2720 ng·h/mL). These data provided PK/pharmacodynamic (PD) correlation and the effective concentration for complete p-KDR inhibition (EC100=181 ng/mL) useful to guide clinical dose selection.

Surufatinib was further evaluated for anti-tumor activity and demonstrated high potency on inhibiting tumor growth in multiple human tumor xenografts, such as gastric cancer BGC-823, non-small cell lung cancer NCI-H460, human renal cell carcinoma Caki-1, and colon cancer HT-29. Surufatinib was orally dosed at 20, 40, and 80 mg/kg twice daily and demonstrated a good dose response in these studies. Among the 4 models, gastric cancer BGC-823 showed the highest sensitivity to surufatinib. The tumor growth inhibition (TGI) achieved 68%, 90%, and 103% at 20, 40, and 80 mg/kg, respectively.

The anti-angiogenesis effect of surufatinib in the anti-tumor efficacy studies was investigated by detecting the changes of endothelial cell marker CD31 (PECAM-1) in tumor tissue by immunohistochemistry technology. Surufatinib significantly decreased the vascular vessel density (CD31) significantly in both NCI-H460 and Caki-1 xenografts. A clear dose-dependent inhibition of surufatinib on angiogenesis in Caki-1 xenograft tumor tissue was observed. The level of CD31 inhibition appeared to correlate with the TGI.

The plasma concentrations of surufatinib were analyzed in BGC-823 tumor bearing mice at the end of the efficacy study after the last dose. AUC increased with the increase of dose from 20 to 80 mg/kg. The minimum efficacious dose was 20 mg/kg twice daily (TGI≥58%, $p<0.05$) in the BGC-823 model (TGI=68%), and the corresponding minimum efficacious exposure, area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$), in plasma was 4712 ng·h/mL. Surufatinib given orally at 80 mg/kg twice daily resulted in tumor regression with an $AUC_{0\text{-}24h}$ of 16444 ng·h/mL. PK/PD analysis indicated that at this dose complete p-KDR inhibition was maintained for more than 16 hours/day.

Safety Pharmacology:

In safety pharmacology studies, no adverse effects were observed on the cardiovascular and respiratory systems as evidenced by the results of a single dose study in anesthetized dogs (highest

dose 60 mg/kg) and the collected electrocardiograms (ECGs) in a 13-week dog repeat-dose toxicity study (highest dose 12 mg/kg/day). The absence of findings on the cardiovascular system in vivo is in-line with the in vitro human ether-à-go-go-related gene (hERG) assay with an IC_{50} of 1.8 μM, which is 46-fold above the clinical maximum plasma concentration (C_{max}) (free) at a dose of 300 mg, indicating a low risk for corrected QT interval(s) (QTc) prolongation. No effect was found on the central nervous system (CNS) in mice at the highest dose tested (400 mg/kg) based on the Irwin's behavior grading and pole-climbing tests. Collectively, the results showed that surufatinib had a low risk of adverse effects on the cardiovascular, respiratory and CNS.

2.1.4.2 Pharmacokinetics

After a single IV dose of 10 mg/kg surufatinib in rats, the plasma elimination $T_{1/2}$ of surufatinib was measured as 2.8 hours, and plasma clearance and apparent V_d were 3.53 L/h/kg and 13.1 L/kg, respectively. Following dosing via oral gavage at low, medium, and high dose levels, the mean value of time to reach maximum concentration was 3.0~4.2 hours. The oral bioavailability was observed to be dose dependent. At the dose level of 10 mg/kg, the bioavailability was just 9.9%. When the dose was increased to 40 mg/kg or above, the bioavailability exceeded 50%. The low bioavailability observed at the low dose level might be associated with the efflux by P-glycoprotein (P-gp) in intestinal epithelial cells.

After a single IV dose of 5 mg/kg in dogs, the plasma elimination $T_{1/2}$ was 3.3 hours, and plasma clearance and apparent V_d were 3.94 L/h/kg and 18.5 L/kg, respectively. Following a single oral dose of 5, 10, and 20 mg/kg, the mean value of time to reach maximum concentration was 3.5 to 4.5 hours. In the dose range of 5 to 20 mg/kg, surufatinib exposure (C_{max} and area under the plasma concentration-time curve from time 0 to time t [AUC_{0-t}]) increased dose-proportionally. Feeding had no obvious effect on the extent and speed of surufatinib absorption. At the oral dose level of 10 mg/kg, the absolute bioavailability was 30.5%.

After administration via oral gavage in rats, surufatinib was distributed widely in various tissues mainly including lung, liver, spleen, adrenal gland, kidney, pancreas, and stomach wall. The lowest drug concentration was observed in brain, indicating poor brain blood penetration. At 24 hours postdose, concentrations in most tissues reduced to 10% or lower than the peak concentrations.

The results of [^{14}C]-surufatinib excretion study revealed that surufatinib was mostly excreted via feces (approximately 80% of the dose, including 40% for bile excretion), and a small amount was excreted via urine (approximately 10% of the dose).

In vitro liver microsomal metabolic stability assays in various species showed high liver extraction of surufatinib. The clearance of surufatinib in liver microsomes was higher in male rats than in female rats. No significant gender difference was observed in other species. In an in vitro liver microsomes incubation study, phase 1 enzymes mediating the metabolism of surufatinib included cytochrome P450 (CYP)3A4/5 (dehydrogenation, N-demethylation), CYP2C8 (dehydrogenation, N-demethylation), CYP2E1 (mono-oxidization), and flavin-containing monooxygenase.

Surufatinib showed weak reversible inhibition against CYP2D6 and CYP3A4/5 with the IC_{50} of 13 μM and 14 μM, respectively. Time-dependent inhibition study of CYP3A4/5 indicated the potential with a k_{inact} [2] of 0.73 min^{-1} and K_I [2] of 163 μM. The results of CYP1A2 and CYP3A4 induction assay in primary human hepatocytes revealed that surufatinib did not significantly induce CYP1A2 at a concentration of 10 μM or CYP3A4 at a concentration of 2 μM. In an in

vitro permeability and efflux transportation assay using Caco-2 cells, it was found that surufatinib might be a substrate of P-gp.

The protein binding rates of surufatinib were found to be 93~96% in plasma of various species, indicating a moderate to high extent of protein binding in plasma.

2.1.4.3 Toxicology

General Toxicology: In single-dose toxicity studies in rats and dogs, no mortality occurred up to the highest dose tested at 2000 mg/kg, indicating a good tolerability following single oral dosing. Repeated-dose toxicity studies were carried out for surufatinib in rats (1-month, 3-month, and 6--month) and dogs (1-month, 3-month, and 9-month), respectively. The No-Observed-Adverse-Effect Level (NOAEL) of surufatinib in the 13-week repeated-dose toxicity was 15 mg/kg/day and 6 mg/kg/day, respectively, in rats and dogs. The toxicokinetic results indicated that the exposures of surufatinib in rats at the NOAEL dose were higher than the exposures at a clinical dose of 300 mg in study 2015-012-00US1. In the repeated-dose toxicity studies, the main target organs were hepatobiliary system (increase of alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBIL] and triglyceride, along with hepatocyte degeneration/necrosis, slight hyperplasia of bile duct), kidney (increase of urea nitrogen and creatinine, diffuse degeneration and swelling of the glomerular capillary endothelial cell, hyaline cast), immune system (decrease of lymphocyte in thymus, spleen, and mesenteric lymph node, splenic white pulp atrophy), hematopoietic system (bone marrow hematopoietic cell decrease), skeletal system effects (chondrocyte hyperplasia and hypertrophy of growth plate with osteodysplasia and broken teeth), pancreas (acinus atrophy), adrenals glands, and uterus atrophy, and corpus luteum necrosis. All effects were fully or partially reversible after a 4-week recovery period apart from the effects on the skeletal system (broken teeth). Taken together, it is worthwhile to note that at high doses surufatinib might cause kidney and gastrointestinal (GI) toxicities. In addition, with extended dosing at lower/tolerated doses, the lymphatic system might be affected. Therefore, during the initial dose escalation phase in humans, attention should be paid to kidney and GI side effects. Adverse effects related to lymphatic system should also be monitored for long-term use of surufatinib. Most adverse events (AEs) may be reduced or resolved by discontinuation of surufatinib treatment.

Genetic Toxicology: Surufatinib was not genotoxic based on the results of a standard panel of in vitro and in vivo genotoxicity studies comprised of an in vitro bacterial reverse mutation assay in *Salmonella typhimurium* (+/- S9), an in vitro chromosome aberration assay in Chinese hamster ovary cells (+/- S9), and an in vivo rat micronucleus test with inclusion of an alkaline comet assay.

Reproductive and development toxicology: In the fertility and early embryonic development implantation study in rats with doses up to 45 mg/kg/day in males and up to 30 mg/kg/day in females, respectively, surufatinib at 30 mg/kg/day affected female reproductive function and embryo formation, and produced uterus damage. The NOAEL for male rat's fertility and early embryonic development was established to be 45 mg/kg/day, and that for female rat's fertility and early embryonic development was 10 mg/kg/day. In the embryo-fetal development study in rats at the top-dose of 15 mg/kg/day, mean maternal body weight gain decrease, an increase in post implantation loss, a reduction in gravid uterine weight, and reductions in adjusted mean fetal body weight were noted. Developmental toxicities observed at 15 mg/kg/day consisted of fetal external malformations, visceral malformations, skeletal malformations and skeletal growth retardation. The NOAEL for both maternal toxicity and fetal development was 4 mg/kg/day. In the embryo-

fetal development study in rabbits, the dose of 48 mg/kg/day interfered with embryo formation and induced growth retardation, the NOAEL of surufatinib for maternal effects was 48 mg/kg/day, and the NOAEL for embryo- fetal toxic effects was 24 mg/kg/day.

In a range-finding juvenile toxicity study, rats were dosed from postnatal (PND) 4 to up to PND 28. Mortality occurred at 10 and 30 mg/kg/day, but not at 3 mg/kg/day. No effects were noted on incisor eruption, developed teeth, or femur length. In the definitive juvenile toxicity study with surufatinib, rats were dosed from PND 10 to PND 70 at doses of 0.5, 1.5, or 3 mg/kg/day. No adverse findings were noted.

Phototoxicity: Surufatinib was not phototoxic based on the results of a phototoxicity study in guinea pigs.

2.1.4.4 Nonclinical Studies for Surufatinib in Combination with Gemcitabine

The combination of surufatinib with gemcitabine offers a unique combination of cellular signaling inhibition (immune modulation and angiogenesis) and inhibition of tumor replicative pathways (perturbed DNA replication) with additive or synergistic potential. A xenograft model of nude mice subcutaneously injected with HT-1080 cells (human fibrosarcoma cell line) demonstrated additive to synergistic effects in TGI of surufatinib in combination with gemcitabine compared to either agent alone. In the anti-tumor efficacy study, surufatinib was administered 80 mg/kg/dose twice daily by oral gavage for consecutive 20 days, and gemcitabine was given once weekly at 3 and 10 mg/kg/dose by IV injection for 3 times.

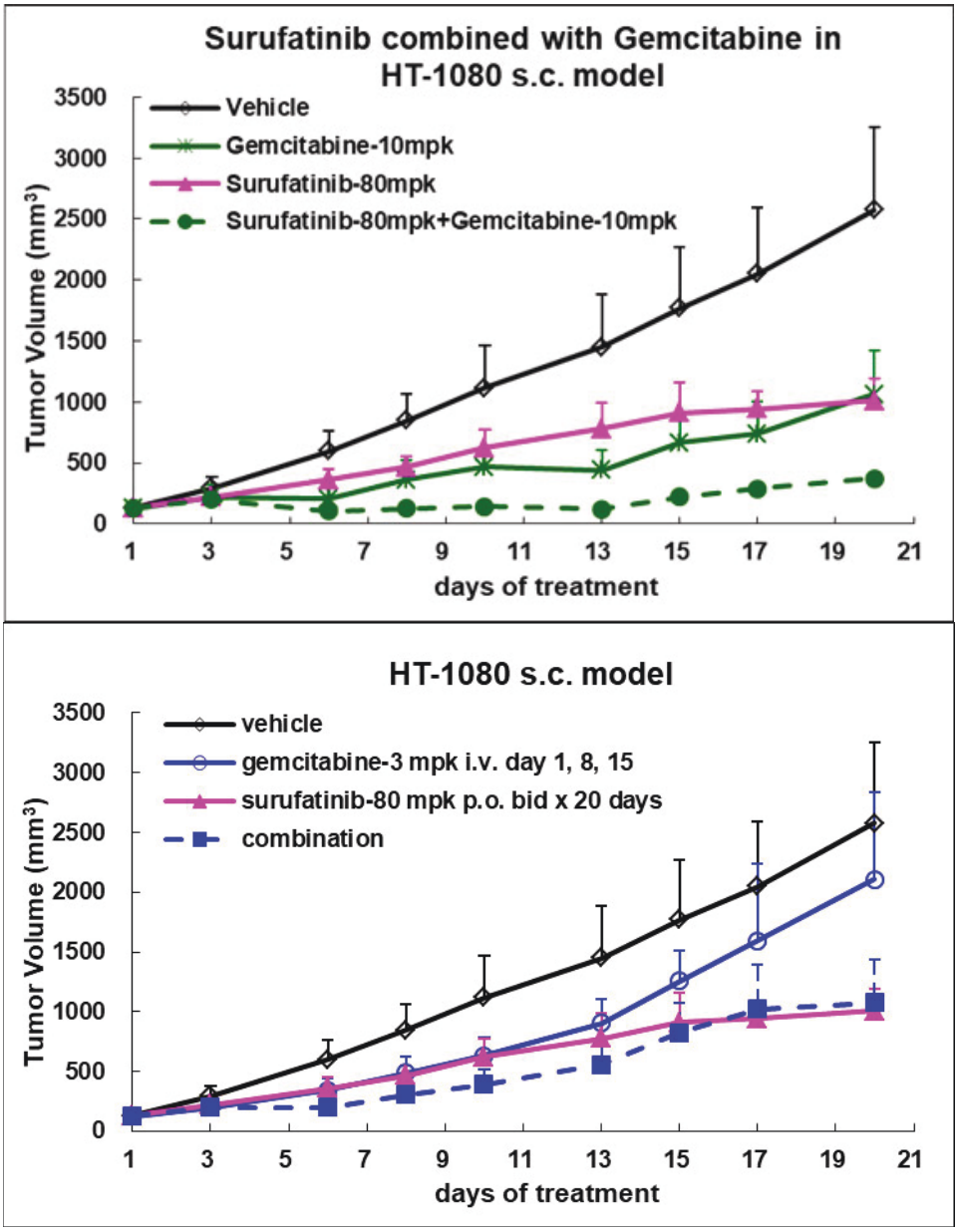
The results (Figure 2) demonstrated that single agent treatment of surufatinib 80 mg/kg/dose and gemcitabine 10 mg/kg/dose led to TGI rates of 64.0% and 61.9%, respectively, while their combination generated a TGI of 90.2%. The statistical significance was observed when combination treatment was compared with either surufatinib or gemcitabine monotherapy on tumor volume changes ($p<0.01$). Based on these mechanisms of action, the combination of surufatinib with gemcitabine is hypothesized to improve the overall efficacy in patients versus monotherapy with either surufatinib or gemcitabine.

Surufatinib at a dose level of 80 mg/kg significantly improved anti-tumor activity of gemcitabine at 10 mg/kg. The enhanced anti-tumor effect by combination treatment might ascribe to simultaneous inhibition of different cell types as well as multiple pathways in tumor microenvironments: gemcitabine killed tumor cells and surufatinib suppressed tumor angiogenesis and TAMs.

The TGIs of gemcitabine 3 and 10 mg/kg decreased from 54% and 84% at day 6 to 19% and 62% at day 20, respectively, suggesting a trend of emerging resistance to gemcitabine and consequently also resulting in a gradually reduced anti-tumor efficacy by combination treatment.

The totality of the safety and efficacy data support the investigational use of surufatinib combined with gemcitabine in pediatric patients with relapsed/refractory disease. These patients have little to no other treatment options and thus the overall benefit risk profile favors investigation of the potential benefits of the combination. Refer to the IB for further information regarding surufatinib nonclinical studies.

Figure 2 Tumor Volume in Fibrosarcoma HT-1080 Model



BID=twice a day; IV=intravenous(ly); MPK=milligram per kilogram; PO=orally; SC=subcutaneously.

2.1.5 Supportive Clinical Data

2.1.5.1 Clinical Pharmacology and Pharmacokinetics

In Chinese patients with cancer, surufatinib was absorbed rapidly, with the concentration reaching maximum level after 1.0 to 2.0 hours of dosing. Mean plasma $T_{1/2}$ ranging from 14.9 to 20.2 hours was observed. Following multiple doses of surufatinib QD, the plasma surufatinib concentration reached steady state 14 days after dosing, with exposure accumulating 1.2- to 2.4-fold at steady state compared to day 1 (2009-012-00CH1 and 2014-012-00CH1). PK results from the US patient population (2015-012-00US1 [ongoing]) showed that surufatinib exposure, in general, increased

proportionally with an increasing dose from 50 to 400 mg QD. There were no meaningful differences in surufatinib exposure between Chinese and US patients (Dasari 2020).

2.1.5.2 Clinical Safety

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2.1.5.3 Clinical Efficacy

Surufatinib has demonstrated statistically significant and clinically meaningful efficacy in 2 completed phase 3 randomized, double-blind, placebo-controlled studies in Chinese patients with advanced extra-pancreatic NET (SANET-ep) and patients with advanced pancreatic NET (SANET-p) and has shown promising anti-tumor activity in a US phase 1 study (2015-012-00US1). The SANET-ep study met its primary endpoint at the planned interim analysis, with significantly improved progression-free survival (PFS) in surufatinib-treated patients compared with placebo-treated patients (median PFS of 9.2 months in surufatinib-treated patients versus 3.8 months in placebo-treated patients; HR 0.334; $p<0.0001$). Similarly, surufatinib-treated patients in the SANET-p study showed a statistically significant improvement in PFS compared with placebo-treated patients (median PFS of 10.9 months in surufatinib-treated patients versus 3.7 months in placebo-treated patients; HR 0.491; $p=0.0011$). In addition to the primary PFS endpoint, SANET-ep and SANET-p demonstrated meaningful improvements in other important efficacy measures such as ORR, disease control rate (DCR), duration of response (DoR), and time to response (TTR).

In Study 2015-012-00US1, patients with biliary tract cancer, extra-pancreatic neuroendocrine tumor (epNET), pancreatic neuroendocrine tumor (pNET), and soft tissue sarcoma (STS) were enrolled. Based on interim analysis for epNET and pNET cohorts, the PFS rate at 11 months for patients with epNETs (16 patients) was 51.1% (95% CI: 12.8, 80.3) and 57.4% (95% CI: 28.7, 78.2) for patients with pNETs (16 patients). The observed median PFS was 11.50 months (95% CI: 6.47, 11.50) and 15.18 months (95% CI: 5.19, Not reached [NR]) for patients with epNETs and pNETs, respectively. An ORR of 6.3% was observed for patients with epNETs and 18.8% for patients with pNETs. A disease control rate of 90.6% (95% CI: 75.0, 98.0) was observed for all NET patients (93.8% epNET; 87.5% pNET). All patients had previously received everolimus and/or sunitinib (Paulson 2021). Enrollment to the STS cohort is ongoing, and no analysis has been performed to date.

2.1.6 Benefit/Risk Assessment

2.1.6.1 Risk Assessment

Overall, nonclinical and clinical study results have demonstrated that surufatinib is safe and well tolerated. Surufatinib is administered orally while gemcitabine will be administered intravenously. Due to the IV administration of gemcitabine, there is the potential risk for pain and local irritation at the infusion site. This will be evident clinically and can be treated symptomatically. The collection of blood for PK sampling may require additional IV access.

Due to the risk of fetal and teratogenic adverse effects as seen in animal studies, pregnant or breastfeeding women will not be entered in this study. Males or females of reproductive potential may not participate unless they have agreed to use 2 effective methods of birth control, including a medically accepted barrier or contraceptive method (eg, male or female condom) for the duration of the study. Abstinence is an acceptable method of birth control. Both males and females with childbearing potential will be fully informed of the lack of reproductive toxicity data, and females of childbearing potential must have a negative pregnancy test prior to enrollment. Legal guardians of all participating children will be informed of the lack of reproductive toxicity data.

Identified risks for surufatinib are hepatic disorder, hemorrhage, hypertension, AKI, proteinuria, leukopenia, anemia, thrombocytopenia, GI symptoms, and hypothyroidism/thyroid stimulating hormone increased. Table 3 presents important and non-important identified risks.

Risks for gemcitabine are hypersensitivity, myelosuppression, pulmonary toxicity, hemolytic uremic syndrome, hepatic toxicity, exacerbation of radiation therapy toxicity, capillary leak syndrome, and posterior reversible encephalopathy syndrome.

Table 3 Summary of Identified Risks of Surufatinib

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AE=adverse event; AKI=acute kidney injury; ALT=alanine transaminase; AST=aspartate aminotransferase; BP=blood pressure; BUN=blood urea nitrogen; γ-GGT=gamma-glutamyl transferase; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SMQ=standardized MedDRA queries; TSH=thyroid stimulating hormone; VEGFR=vascular endothelial growth factor receptor.

2.1.6.2 Benefit Assessment

Surufatinib may have the potential to provide benefit in the form of decreased tumor burden and/or a reduction in cancer-related symptoms in children, adolescents, and young adults with a variety of advanced solid malignancies who would otherwise have no known curative treatment options.

2.1.6.3 Overall Benefit/Risk Conclusion

The main risk to participants in this study is drug toxicity. This protocol involves greater than minimal risk to children, adolescents, and young adults but presents the potential for direct benefit to individual patients. Potential side effects of surufatinib and gemcitabine are outlined in the protocol and in the IB. Patients on this study may directly benefit from participation. Patients will have been judged to be incurable with standard and alternative therapies, which they are eligible to receive. The intent of this study is to determine a safe and tolerable dose and ultimately to produce a therapeutic tumor response, which would offer the potential for direct benefit to individual patients.

As described, the study design aims to minimize potential risks and although the potential benefits in patients are unknown at this time, nonclinical and clinical data demonstrate evidence of anti-tumor activity. Thus, the benefit/risk assessment for this first time in children study appears acceptable for patients for whom there is no alternative standard therapy.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

2.2 Study Rationale

Pediatric patients with recurrent or refractory solid tumors continue to experience dismal outcomes despite advances through much of pediatric oncology. There is an unmet need for better treatments for pediatric patients with solid tumors. This study will be performed on pediatric patients with recurrent or refractory solid tumors who have no known curative therapy.

Although surufatinib monotherapy has shown clinical activity in adults with NET and in select adult cancer models, this study proposes that adding a chemotherapy agent in combination with surufatinib will provide added benefit for pediatric patients with refractory/recurrent solid tumors. Many current pediatric early phase studies combine an investigational agent with an irinotecan/temozolomide backbone both for anti-tumor effect and because of the tolerability and non-overlapping toxicities of the irinotecan/temozolomide backbone. However, irinotecan and temozolomide have shown limited effect in patients with osteosarcoma, a population of patients who may benefit most from a CSF-1R inhibitor such as surufatinib.

2.2.1 Combination Therapy with Gemcitabine

Gemcitabine was chosen as the combination partner to surufatinib for pediatric development based upon 3 major factors: (1) well tolerated with a manageable toxicity profile, (2) minimal overlapping toxicities with surufatinib, and (3) demonstrated activity in a multitude of tumors. An acceptable toxicity profile is a critical characteristic in the proposed population of patients with relapsed/refractory pediatric malignancies, as these patients will have been heavily pre-treated with resultant lingering toxicities such as limited bone marrow reserve. The tolerability profile

permits gemcitabine to be co-administered with targeted agents such as surufatinib. Gemcitabine has been combined with other TKIs, specifically antiangiogenic agents similar to surufatinib such as pazopanib, sunitinib, and axitinib, and shown to be both effective and safe (Duska 2020, Michaelson 2015, Park 2019).

Gemcitabine alone, in combination with cytotoxic agents and in combination with targeted agents, has demonstrated clinical benefit in patients with sarcoma.

Although gemcitabine has not been approved in the US or the EU/UK for the treatment of pediatric tumors, it is well known to be utilized in the treatment of a variety of pediatric malignancies including soft tissue and bone sarcomas (Pushpam 2020). Several consensus guidelines for the treatment of sarcoma list gemcitabine (monotherapy or in combination) as treatment options: (1) The National Comprehensive Cancer Network (NCCN), (2) European Society for Medical Oncology – European Network for Rare Adult Solid Cancer (ESMO-EURACAN) Clinical Practice Guidelines, and (3) The Systemic Anti-Cancer Therapy (SACT) database for sarcoma in the United Kingdom (Dangoor 2016).

As a single agent, gemcitabine has modest activity in pediatric tumors. In the pediatric phase 1 study of gemcitabine involving 40 patients with disease refractory to conventional therapy: 1 patient with a pancreatic tumor achieved a partial response (PR), 4 of 13 patients with osteogenic sarcoma had SD, and 1 of 4 patients with Ewings had SD for 17 months (Reid 2004). Despite low rates of objective responses, in the context of disease refractory to standard of care agents, SD is an indicator of anti-tumor activity in this heavily pre-treated patient population.

More recently, gemcitabine has been studied in combination with other cytotoxic agents such as docetaxel resulting in slightly increased anti-tumor activity. In a phase 2 study of gemcitabine and docetaxel in patients with recurrent Ewing sarcoma, osteosarcoma, or chondrosarcoma; PRs were observed in 1 of 14 patients with osteosarcoma, 2 of 14 patients with Ewing sarcoma, and 2 of 25 patients with chondrosarcoma (Fox 2012). The increased activity did however, come at a cost of increased toxicity. Dose modifications for toxicity were required for 8 patients in cycles 1 and 16 patients in subsequent cycles. Furthermore, 7 patients withdrew due to toxicity.

This observation of enhanced anti-tumor activity for the combination of gemcitabine and docetaxel counter balanced by increased toxicity was confirmed in a phase 2 study conducted in adults with soft tissue sarcoma (Maki 2007). Patients were randomized to either combination therapy with gemcitabine and docetaxel or gemcitabine monotherapy. Objective responses (16% gemcitabine/docetaxel versus 8% gemcitabine) and median PFS (6.2 months gemcitabine/docetaxel versus 3.0 months gemcitabine) were both found to be superior for the combination. However, significant toxicity was higher for the combination; the posterior probability of the combination having a shorter time to discontinuation for toxicity compared to gemcitabine alone was 0.999. The Investigators concluded that gemcitabine/docetaxel yields superior anti-tumor activity but with increased toxicity. Notably, this safety profile was observed in patients who received only 0 to 3 prior lines of therapy. One would expect to see a worse tolerability profile of the combination in a more heavily pre-treated population, as is proposed in this initial pediatric study plan.

Gemcitabine has also been paired with targeted agents with encouraging results. In a randomized phase 2 study in refractory soft tissue sarcoma, pazopanib + gemcitabine was shown to significantly improve PFS over pazopanib alone (HR 0.58; 95% CI 0.36, 0.92; p=0.02) (Schmoll 2021). Similar results were reported in a population of 148 patients with recurrent ovarian cancer:

median PFS was 5.3 months for pazopanib + gemcitabine versus 2.9 months gemcitabine and overall response was also higher for the combination (20% versus 11%) (Duska 2020). The PFS benefit was most pronounced for the subpopulation with platinum refractory disease (5.32 versus 2.33 months; $p<0.001$), which is potentially applicable to pediatric patients who have been previously treated with platinum agents as part of standard of care.

Furthermore, in a randomized phase 2 study of gemcitabine + pazopanib versus gemcitabine + docetaxel in patients with nonadipocytic soft tissue sarcoma, similar response rates as well as median PFS were observed for both arms (Somaiah 2021). These data suggest gemcitabine combined with a targeted agent could potentially have similar efficacy as the combination of gemcitabine and docetaxel. Of note, the combination of gemcitabine/pazopanib had a favorable safety profile: the rate of related Grade ≥3 AEs was 82% for the gemcitabine/docetaxel arm and 78% for the gemcitabine/pazopanib.

Gemcitabine is a pyrimidine antimetabolite that inhibits tumor growth by disrupting DNA replication. Gemcitabine has been used as salvage chemotherapy alone and in combination in pediatric patients with relapsed/refractory sarcomas, particularly in patients with osteosarcoma but also in those with Ewing sarcoma or RMS (Mora 2009, Rapkin 2012). In phase 1 testing of gemcitabine in pediatric patients, no maximum tolerated dose (MTD) was reached, with only 1 in 6 patients experiencing Grade 4 myelosuppression when treated with 2100 mg/m^2 of gemcitabine once weekly for 2 weeks in 28-day cycle (Reid 2004). Gemcitabine has also been used safely in combination with nab-paclitaxel in pediatric patients with relapsed/refractory sarcomas at a dose of 1000 mg/m^2 using a 2-week dosing interval (Metts 2018). In another example of gemcitabine in combination therapy, a recent Children's Oncology Group study (AHOD1221) combined gemcitabine with brentuximab and was well tolerated at a dose of 1000 mg/m^2 on days 1 and 8 (Cole 2018). Complete response (CR) was observed in 24 (57%) of 42 evaluable patients as well as 13 patients with PR or SD within the first 4 cycles of treatment (Cole 2018). Gemcitabine has also been combined with docetaxel and bevacizumab in relapsed and refractory pediatric sarcoma patients and shown good tolerability and encouraging anti-tumor activity: 2 of 3 patients had a PR and the third patient had SD for >6 months (Higorani 2012). Lastly, gemcitabine combined with carboplatin and the CSF-1R inhibitor MCS110 is under active investigation in adults with triple negative breast cancer (NCT02435680) (Cannarile 2017).

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

	Objectives	Endpoints
Primary	• To determine MTD and/or RP2D of surufatinib, and to evaluate the safety and tolerability of surufatinib in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma	• The incidence of dose limiting toxicities in each dose level • Safety, as assessed by: o The frequency and severity of AEs o Physical examination findings o Vital signs o Laboratory test results o 12-lead ECG
Secondary	• To characterize the PK of surufatinib as a monotherapy and in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma	• Pharmacokinetic parameters for the dose escalation and PK expansion cohorts: C_{max}, T_{max}, AUC, C_{min}, effective $T_{1/2}$, CL/F, and accumulation ratio
	• To evaluate the anti-tumor activity of surufatinib in combination with gemcitabine in pediatric patients with recurrent/refractory solid tumors or lymphoma	• Efficacy endpoints evaluated per RECIST version 1.1: o ORR o DCR o TTR o Duration of response (DoR) o PFS
	• Acceptability and palatability of surufatinib oral suspension	• The taste and palatability survey

AE=adverse event; AUC=area under the plasma concentration-time curve; CL/F=apparent total clearance from plasma after oral administration; C_{max}=maximum plasma concentration; C_{min}=minimum plasma concentration; DCR=disease control rate; DoR=duration of response; ECG=electrocardiogram; MTD=maximum tolerated dose; ORR=objective response rate; PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=Recommended Phase 2 Dose; $T_{1/2}$=half-life; T_{max}=time to reach the maximum plasma concentration; TTR=time to response.

4 STUDY DESIGN

Design of the study is presented in the study schematic (Figure 1).

Overall Design

This is an open-label, multicenter, phase 1/2 study of surufatinib in combination with gemcitabine in pediatric, adolescent, and young adult patients with recurrent or refractory solid tumors. This study design allows for dose escalation with intensive safety monitoring to ensure the safety of all patients. This study will utilize a rolling 6 design, with 3 dose escalation levels and 1 de-escalation level, if needed. The MTD and/or the RP2D will be designated in pediatrics.

4.1 Dose Escalation

This is a dose escalation study with sequential dose escalation of surufatinib in combination with gemcitabine. Patients with any recurrent or refractory solid tumors or lymphoma, who have a known or expected dysfunction of VEGFR-1, -2, and -3; FGFR-1; or CSF-1R pathways may be enrolled. The first study cycle will be 35 days. During cycle 1, surufatinib will be administered, orally, QD, as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine intravenously on days 15 and 22. All subsequent cycles will be 21 days per cycle, where surufatinib will be administered orally, QD, and gemcitabine administered intravenously on days 1 and 8. The starting dose of surufatinib will be 120 mg/m^2 daily, which is approximately 70% of the adult single agent RP2D of 175 mg/m^2 (300 mg/day normalized to standard adult BSA of 1.71 m^2). Gemcitabine (1000 mg/m^2 weekly × 2 doses) will not be escalated and will be given on days 15 and 22 of cycle 1 and then on days 1 and 8 of all subsequent cycles. Surufatinib will be given continuously on days 1 to 35 in cycle 1. The first 14 days of cycle 1 serves to assess tolerability and toxicity of single agent surufatinib.

This study also includes a PK expansion cohort to be conducted at the presumed RP2D/MTD that is established in the dose escalation portion of the study. The PK expansion cohort will consist of up to 6 patients at each of the following 2 strata: patients <12 years of age and patients 12 to <18 years of age based on age at the time of enrollment. Surufatinib PK profiles after the first dose and at steady state will be characterized in both dose escalation cohort and PK expansion cohort. Patients who are treated at the RP2D/MTD in dose escalation cohort will be counted in the PK expansion cohort. For Spain only: No subjects will be allowed on the study with a BSA ≤0.6 or body weight ≤14 kg.

4.1.1 Dose Finding Period

The dose finding period, which is the timeframe to define dose limiting toxicity (DLT), begins with the initial dose of surufatinib and ends on the last day of cycle 1. Should there be a delay (maximum 7 days delay) starting the subsequent cycle, dose finding will complete on the start date of the subsequent cycle.

Dose escalation and de-escalation rules:

The study will utilize the rolling 6 design (Skolnik 2008). Within a dose level cohort, up to 6 patients may be concurrently enrolled, accrual will only be suspended when awaiting data from 6 patients. Dose level assignment will be determined based on the number of patients currently enrolled in the dose level, the number of DLTs observed, and the number of evaluable patients at

risk for developing a DLT. Dose escalation/de-escalation rules are as follows, and in Table 5 below:

1. If 2 or more patients experience DLTs in dose level 1 then the dose will be considered not tolerated and there will be a de-escalation to dose level -1.
2. If 2 or more patients experience DLTs in dose levels 2 or 3 then the dose will be considered not tolerated and the prior dose level will be considered the MTD and will become the RP2D.
3. If 3 patients are enrolled in a dose cohort with no DLTs, then the next patient enrolled will be enrolled in the subsequent dose level.
4. If toxicity data is not yet available for 1 or more of the first 3 patients, then the next patient enrolled will be enrolled at the same dose level.
5. If a patient is not evaluable (NE) for toxicity, then they will be replaced in the same dose level with the next available patient.
6. The start of dosing in the subsequent cohort will not begin until the prior cohort has been evaluated and it has been determined that the MTD has not been exceeded.
7. There will be no intra-patient dose escalations.
8. The MTD/RP2D will be the dose level at which less than one-third of evaluable patients (dose escalation and PK expansion cohorts) experience a DLT in cycle 1. If the MTD determined in dose escalation cohort is considered not tolerable, additional patients will be enrolled to the PK expansion cohort at the next lower dose level.

Table 5 Rolling 6 Dose Escalation Rules Based on DLT Evaluable Patients

Total Number of Patients Enrolled at Dose Level	Number of Patients with DLT	Number of Patients Without DLT	Number of Patients with Data Pending	Decision
2	0 or 1	0, 1, or 2	2, 1, or 0	Same dose level
2	2	0	0	De-escalate[a]
3	0	0, 1, or 2	3, 2, or 1	Same dose level
3	0	3	0	Escalate[b]
3	1	0, 1, or 2	2, 1, or 0	Same dose level
3	≥2	0 or 1	1 or 0	De-escalate[a]
4	0	0, 1, 2, or 3	4, 3, 2, or 1	Same dose level
4	0	4	0	Escalate[b]
4	1	0, 1, 2, or 3	3, 2, 1, or 0	Same dose level
4	≥2	0, 1, or 2	2, 1, or 0	De-escalate[a]
5	0	0, 1, 2, 3, or 4	5, 4, 3, 2, or 1	Same dose level
5	0	5	0	Escalate[b]
5	1	0, 1, 2, 3, or 4	4, 3, 2, 1, or 0	Same dose level
5	≥2	0, 1, 2, or 3	3, 2, 1, or 0	De-escalate[a]

Table 5 Rolling 6 Dose Escalation Rules Based on DLT Evaluable Patients

Total Number of Patients Enrolled at Dose Level	Number of Patients with DLT	Number of Patients Without DLT	Number of Patients with Data Pending	Decision
6	0	0, 1, 2, 3, or 4	6, 5, 4, 3, or 2	Suspend pending review
6	0	5 or 6	1 or 0	Escalate[b]
6	1	0, 1, 2, 3, or 4	5, 4, 3, 2, or 1	Suspend pending review
6	1	5	0	Escalate[b]
6	≥2	0, 1, 2, 3, or 4	4, 3, 2, or 1	De-escalate[a]

DLT=dose limiting toxicity; MTD=maximum tolerated dose.

[a] If 6 patients already enrolled at the next lower dose level, the MTD has been defined.

[b] If the highest dose level has been reached, the recommended dose has been reached.

Safety monitoring and evaluation of dose escalation will be carried out by the Safety Review Committee (SRC). The SRC will determine whether it is safe to continue to the next predefined dose level, stay at the currently assigned dose level, or whether the dose should be de-escalated to a lower dose level and finally to determine the MTD/RP2D. Additional details are outlined in Section 11.1.

At the MTD/RP2D, a PK expansion cohort will be planned to ensure that up to 6 patients <12 years of age and 6 patients ≥12 and <18 years of age have been evaluated at the MTD/RP2D. This will allow the study to explore further the safety, tolerability, and PK at this dose.

4.2 Definition of Dose Limiting Toxicity

Dose limiting toxicity will be defined as any of the following events that are attributable to protocol therapy (at least possibly related). Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The NCI CTCAE provides descriptive terminology and a grading scale for each AE listed.

Any suspected or confirmed DLT is to be reported within 24 hours of learning of the event. Determination of **a DLT will be made by the Investigator and the Sponsor's monitor**. Patients who discontinue their study treatment for any reason other than DLT (eg, early disease progression) during cycle 1 and have not received at least 80% (28 of total 35 doses) of the prescribed oral surufatinib dose and both doses of gemcitabine prior to discontinuation will be replaced with another patient at the same dose level.

Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The DLT monitoring and evaluation period for consideration of dose escalation/de-escalation will be the first cycle of treatment. Should there be a delay (maximum 7 days delay) starting the subsequent cycle, dose finding will complete on the start date of the subsequent cycle. Toxicities with subsequent cycles will be monitored, and if a significant number of delayed toxicities are observed, the Sponsor will consider an amendment to include delayed toxicities in assessing the MTD.

Dose limiting hematological and non-hematological toxicity are defined differently.

Non-Hematological DLT:

- Any Grade 3 or greater non-hematological toxicity attributable to the protocol therapy with the specific exception of:
  - Grade 3 nausea, vomiting, or diarrhea recovering to ≤Grade 1 within 3 days after supportive therapy is administered
  - Grade 3 weight loss
  - Grade 3 or 4 fever <5 days in duration
  - Grade 3 infection <5 days in duration
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation within 7 days
  - Grade 3 proteinuria (urine P/C [protein/creatinine] ratio >1.9) unless confirmed with a second measurement within 72 hours
  - Grade 3 pruritus <5 days in duration
  - Grade 3 fatigue <5 days in duration
- Grade 3 liver enzyme elevation including ALT/AST (up to 10 × the upper limit of normal (ULN) in the setting of normal bilirubin) that returns to Grade ≤1 or baseline within 7 days without holding study drug will NOT be considered a DLT
  - Grade 3 AST/ALT elevation >10 × ULN will be considered a DLT
  - Any Grade 3 AST/ALT duration of ≥8 days will be considered a DLT
- Cases of Hy's law (ALT or AST >3 x ULN along with TBIL >2 x ULN without evidence of cholestasis) will be considered a DLT if no other reason can be found to explain the observed injury (e.g., infection, malignancy, another drug capable of causing the liver injury, etc.)
- Any Grade 2 non-hematological toxicity that persists for ≥7 days and is considered medically significant or intolerable by the patient that requires treatment interruption
- Dose limiting hypertension (see Appendix 7)
  - Any Grade 4 hypertension
  - A systolic or diastolic blood pressure (BP) >5 mmHg above the 99th percentile (ie, Grade 3) confirmed by repeated measurement on the same day is dose limiting if BP does not return to < ULN (Grade 1) within 14 days of initiation of antihypertensive medication. For patients ≥18 years old, Grade 3 is defined as a diastolic BP ≥100 mmHg or a systolic BP ≥160 mmHg
- Grade 3 QTc prolongation >500 ms that persists despite correction of serum electrolyte abnormalities will be considered dose limiting

Hematological DLT:

- In patients evaluable for hematological toxicity, DLT is defined as:
  - Grade 4 thrombocytopenia (platelets <25 000/mm^3) for >7 days, or requiring a platelet transfusion on 2 separate days within a 7-day period regardless of association with bleeding
  - Grade 3 thrombocytopenia (platelets 25 000 – 50 000/mm^3) with clinically significant bleeding

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3) that lasts for >7 days
- Cycle 1, days 15 and 22:
  - Grade 4 neutropenia (ANC <500/mm^3) that does not resolve to ANC ≥750/mm^3 within 3 days will be considered dose limiting.
- Myelosuppression that causes a delay of >7 days for start of cycle 2
- Exception:
  - Grades 3 and 4 febrile neutropenia will not be considered a DLT.

DLT-Equivalent:

- DLT-equivalent is defined as any AE meeting criteria for DLT that occurs outside the DLT evaluation period (cycle 1)

4.3 Design Rationale

The dose finding study is designed to provide safety and tolerability data of surufatinib in combination with gemcitabine in pediatric patients. Cycle 1 will aim to evaluate the tolerability, safety, and PK profile of surufatinib as a single agent and in combination with gemcitabine. The maximum dose of surufatinib will not exceed 300 mg/day in any arm of the study as it is the RP2D for adults.

This study will utilize a rolling 6 design with 3 dose escalation levels and 1 de-escalation level, if needed. Surufatinib starting dose will be 120 mg/m^2 daily, which is approximately 70% of the adult single agent RP2D of 175 mg/m^2 (300 mg/day normalized to standard adult BSA of 1.71 m^2). Gemcitabine (1000 mg/m^2 weekly × 2 doses) will not be escalated, and will be given on days 15 and 22 of cycle 1, and then days 1 and 8 of all subsequent cycles. Surufatinib will be given continuously on days 1 to 35 in cycle 1. The first 14 days of cycle 1 serves to assess tolerability and toxicity of single agent surufatinib. At MTD and/or RP2D, a PK expansion cohort will be planned to assure that up to 6 patients <12 years of age and 6 patients ≥12 and <18 years of age have been evaluated at the MTD/RP2D.

The rolling 6 design allows for reduction of the overall study duration by decreasing the number of times that enrollment is suspended for toxicity evaluation. Toxicity will be assessed using the NCI CTCAE version 5.0, except for study sites in the US, for AST/ALT, grading in Appendix 8 will be used. Tumor assessments will be conducted according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria at screening, and throughout the study according the Schedule of Events outlined in Table 1. Confirmation of CR and PR is required at no less than 4-week intervals between the date of initial response and the confirmation assessment date.

5 POPULATION

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study before starting study treatment. Under no circumstances can there be exceptions to this rule.

5.1 Recruitment

As of 16 December 2022, enrollment to study 2020-012-GLOB2 was halted based upon the strategic evaluation of the clinical development of surufatinib in the United States and Europe with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to surufatinib treatment. Currently enrolled patients who are deriving clinical benefit from treatment with surufatinib may continue to participate in the study as per the protocol. There is no planned interruption in the supply of surufatinib to clinical trial sites with active patients. In addition, as no patients have enrolled in study Part 2 (dose expansion) as of the end of enrollment date, Part 2 is removed from the study design in this protocol Amendment 3. Part 1 will continue as outlined in this protocol amendment.

This study will be offered to pediatric patients. Anticipated number of patients is as below:

- Total: maximum 36 patients over approximately 2 years
- Rolling 6 design with 3 planned dose escalation levels: 6×3=maximum 18 patients
- One dose de-escalation if starting dose is intolerable: minimum 4 patients
- PK expansion cohort up to 12 patients (6 patients <12 years of age and 6 patients ≥12 and <18 years of age)
- 15% unevaluable rate: 6 patients (maximum 36 patients)

5.2 Definitions

Patients officially enter the screening period following provision of informed consent either directly or via a legally authorized representative.

A screen failure is a consented patient who has been deemed ineligible on the basis of one or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may be rescreened no earlier than 7 days after the date of screen failure. Screen failures may be rescreened once.

An enrolled patient is one who has been deemed eligible and has been assigned an anticipated treatment start date.

5.3 Inclusion Criteria

To be included in this study, each individual must satisfy all of the following criteria:

1. Age: At time of study enrollment, patients must be

   For US sites:

   a. ≥2 and <18 years of age;

   For EU/UK sites:

   a. From birth to <18 years of age;

2. Diagnosis:

a. Patients with any recurrent or refractory solid tumors or lymphoma (not CNS) that have a known or expected dysfunction of VEGFR-1, -2, and -3; FGFR-1, or CSF-1R pathways (based on literature) are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

3. Disease status: Patients must have measurable or evaluable disease
4. Therapeutic options: Patient's current disease state must be one for which there is no known curative therapy.
5. Performance level: Karnofsky ≥50 for patients ≥16 and <18 years of age and Lansky ≥50 for patients <16 years of age (see Appendix 1), Eastern Cooperative Oncology Group (ECOG) ≤2 for patients ≥18 years of age. (Note: Patients who are unable to walk because of paralysis, but who are using a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.)
6. Organ function requirements

   Adequate organ and bone marrow function as defined below:

   a. ANC ≥750/mm^3
   b. Platelets ≥75000/mm^3: patients must be transfusion independent and should not have received a platelet transfusion within 5 days of enrollment
   c. Hemoglobin ≥8.0 g/dL: patients may have received packed red blood cell transfusion at any time prior to enrollment, but hemoglobin must remain ≥8.0 g/dL for at least 7 days following transfusions
   d. Serum creatinine based on age/sex as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 to <2 years	0.6	0.6
2 to <6 years	0.8	0.8
6 to <10 years	1	1
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating glomerular filtration rate (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the Centers for Disease Control and Prevention.

   e. Total bilirubin ≤1.5 × ULN for age. For patients with primary liver malignancy or liver metastases or patients with documented/suspected Gilbert's disease, TBIL ≤3 × ULN.
   f. In patients with no liver metastases: AST and ALT ≤3 × ULN (Please reference Appendix 8 for the ULN of AST and ALT for the study sites in the US.)
   g. In patients with liver metastases: AST or ALT ≤5 × ULN.
   h. Serum albumin ≥2 g/dL.
   i. Urine dipstick ≤1+ for protein or ≤30 mg/dL in urinalysis, unless quantitative protein is <1000 mg in a 24-hour urine sample or urine P/C ratio on spot urine testing is <0.5.

j. Adequate cardiac function as indicated by the following:

- Shortening fraction of >27% by echocardiogram or left ventricle ejection fraction of ≥55% by radionuclide angiogram (multigated acquisitions, [MUGAs])
- No clinically significant cardiac arrhythmias, stroke, or myocardial infarction within 6 months prior to enrollment
- QTcF ≤480 ms

7. Patients with known bone marrow metastatic disease will be eligible for the study provided they meet the blood counts in the inclusion criteria (may receive transfusions provided that they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients must be evaluable for hematologic toxicity for the dose escalation part of the study (cycle 1). If dose limiting hematologic toxicity is observed, all subsequent patients enrolled at the same dose level must be evaluable for hematologic toxicity.
8. Adequate BP control which is defined as a BP <95th percentile (≤Grade 1) for age, height, and sex. Please note that 3 serial BP readings should be obtained and averaged to determine baseline BP. A patient's condition may be controlled on no more than 1 antihypertensive medication and must be on a stable dose for at least 7 days prior to treatment initiation.
9. Prior therapy: Patients must have fully recovered from the acute toxic effects of all prior anticancer therapy and meet minimum durations from prior anticancer therapy prior to enrollment.

a. Myelosuppressive therapy: the patient must not have received myelosuppressive chemotherapy within 3 weeks prior to the first dose of study treatment.

- Exception: patients who have had vincristine need to have a washout of at least 7 days prior to the first dose of study treatment.

b. Hematopoietic growth factors: at least 7 days must have elapsed since the completion of therapy with a growth factor; at least 14 days must have elapsed after receiving pegfilgrastim.
c. Anticancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or ANC): ≥7 days after the last dose of agent.
d. Antibodies: ≥21 days must have elapsed from infusion of the last dose of antibody and toxicity related to prior antibody therapy must be recovered to Grade ≤1.
e. Radiotherapy: ≥2 weeks must have elapsed since local palliative radiation therapy (small port); ≥6 weeks must have elapsed since treatment with therapeutic doses of metaiodobenzylguanidine (MIBG); ≥3 months must have elapsed if prior craniospinal XRT was received, if ≥50% of pelvis was irradiated, or if total body irradiation (TBI) was received; ≥6 weeks must have elapsed if other substantial bone marrow irradiation was given.
f. Stem cell rescue: ≥2 months must have elapsed since autologous transplant.
g. Patients must not have received prior exposure to surufatinib.
h. Patients may have received gemcitabine previously but must not have had radiographic progression of disease during prior gemcitabine chemotherapy.

10. Informed consent: Provision of signed and dated written informed consent (parent/legal guardian if patient <18 years of age) and assent (from patients aged >7 years) prior to any study-specific procedures, sampling, and analyses.

11. Reproductive potential: Female patients must either be of nonreproductive potential or must have a negative serum pregnancy test upon study entry. Female patients of childbearing potential and male patients with partners of childbearing potential agree to use a highly effective form(s) of contraception that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period, and for 6 months after taking the last dose of study drug. Such methods include oral, progestogen only, hormonal contraception (combined estrogen/progestogen should be avoided) or highly effective non-oral hormonal contraception (eg, Depo-Provera and Implanon) associated with inhibition of ovulation together with a barrier method (eg, diaphragm, always containing a spermicide), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or sexual abstinence in line with the preferred and usual lifestyle of the subject. Oral and non-oral hormonal contraception should always be combined with an additional contraceptive method (ie, barrier method) because of a potential interaction with the study drug. The same criteria are applicable to male patients involved in this clinical study if they have a partner of childbirth potential, and male patients must always use a condom. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (ie, ≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of the ovaries and/or uterus).

5.4 Exclusion Criteria

If a patient meets any of the following criteria, he or she is ineligible for this study:

1. Pregnancy or breastfeeding: Pregnant or breastfeeding females will not be entered into this study due to risks of fetal and teratogenic AEs as seen in animal toxicity studies. Pregnancy tests must be obtained in females who are postmenarchal.
2. Concomitant medications
    a. Corticosteroids: patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible (if used to modify immune AEs related to prior therapy, ≥14 days must have elapsed since last dose of corticosteroid).
    b. Investigational drugs: patients who are currently receiving another investigational drug are not eligible.
    c. Anticancer agents: patients who are currently receiving other anticancer agents are not eligible.
    d. QTc agents: patients who are receiving drugs that prolong QTc (Appendix 5) within the last 7 days are not eligible.
    e. Patients may not be on clozapine, natalizumab, leflunomide, tofacitinib, or warfarin as these may interact with gemcitabine.
    f. Patients who are receiving medications that are strong inhibitors or inducers of CYP3A4 (Appendix 4)
3. Thyroid replacement therapy: Patients who require thyroid replacement therapy are not eligible if they have not been receiving a stable replacement dose for at least 3 weeks prior to study enrollment.
4. Patients who have uncontrolled infection are not eligible.

5. Patients who have major surgery or significant traumatic injury within 28 days of the first dose of study treatment are not eligible.
    a. Central line placement or subcutaneous port placement is not considered major surgery. External central lines must be placed at least 3 days prior to enrollment and subcutaneous ports must be placed at least 7 days prior to enrollment.
6. Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy and without clinical imaging evidence of SD for 14 days or longer; patients requiring steroids for CNS edema within 4 weeks prior to start of study treatment will be excluded.
7. Prothrombin Time (PT) >1.5 × ULN or international normalized ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) >1.5 × ULN.
8. Has a history of allergies to any ingredient of surufatinib or its capsule shell, including tartrazine (E 102).
9. Has a history of allergies to the active ingredient of gemcitabine or to any of the excipients.
10. For Spain only: Has a BSA less ≤0.6 or body weight ≤14 kg.

6 STUDY CONDUCT

The DLT evaluation period for each patient will be 35 days (first cycle), or until the start date of cycle 2 if the start of subsequent cycle is delayed. Patients will be administered with surufatinib in combination with gemcitabine. Surufatinib will be administered daily. Gemcitabine will be administered as an IV infusion on days 15 and 22 of cycle 1 then on days 1 and 8 of all subsequent cycles (21 days per cycle). Patients will be allowed to continue treatment for a maximum of 17 cycles if they meet criteria to continue treatment and are receiving clinical benefit in the opinion of the Investigator. Tumor evaluation and safety assessments will continue through to the completion of treatment.

Patients can remain on treatment until completing cycle 17, or until progressive disease, unacceptable toxicity, or death; whichever comes first. If any patient completes 17 cycles and is still benefiting from study treatment, the Principal Investigator (PI) and Sponsor may discuss options that allow the patient to continue to receive treatment.

6.1 Study Procedures

6.1.1 Screening Period

The screening period will last up to 28 days. Informed consent must be signed prior to any study-specific screening evaluations.

All clinical and laboratory assessments to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the schedule of events. The following laboratory tests need not be repeated at cycle 1 day 1 if therapy starts within 72 hours of obtaining laboratory test to assess eligibility: complete blood count (CBC) with differential, bilirubin, ALT, and serum creatinine.

Imaging studies must be obtained within 28 days prior to start of protocol therapy. Patients with bone marrow involvement must also have a bone marrow biopsy within 14 days prior to the start of protocol therapy.

6.1.1.1 Informed Consent

All patient must sign the informed consent form (ICF) prior to any study-related examinations or protocol procedures. Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

6.1.1.2 Medical History

A complete medical history, including the patient's medical history, disease history, and prior therapies for disease prior to signing of the ICF, should be recorded at screening. Comorbidities that began prior to signing the ICF should be recorded and followed as medical history.

6.1.1.3 Demographics

Demographic characteristics, including date of birth, sex, ethnic group/race, and any relevant lifestyle habits should be recorded at screening and in the applicable electronic case report form (eCRF) (as permitted by local regulations).

6.1.1.4 Performance Score

The Lansky or Karnofsky Performance Score (see Appendix 1), or ECOG Performance Status will be used to assess patient's functional impairment.

6.1.1.5 Tumor Diagnosis and Treatment History

Tumor diagnosis should include the date of primary diagnosis and its type, disease stage, the date of first metastasis, type of previous treatment, start and end dates, best overall response (BOR), and date of PD.

The patient's history of radiation therapy, including the start and end date/s and the site of radiation must be recorded. Surgical history, including operations and less-invasive diagnostic or therapeutic procedures (such as GI endoscopy, biopsy, etc.), the start and end date/s, and name of each procedure and operation site must also be recorded at screening and in the appropriate eCRF.

6.1.1.6 Concomitant Medication and Procedures

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient. All concomitant medications within 28 days before first dose must be recorded in the applicable eCRF, including the generic name of the drug and daily dose, the reason/s for using the medication, as well as the start and stop dates of the medication. Concomitant medications should be reviewed prior to each cycle during the study according to the schedule in Table 1.

6.1.2 Safety Assessments

The following procedures will be performed according to the schedule in Table 1. All assessments must occur within ±3 days (±1 day during cycle 1) from the scheduled date, unless otherwise noted.

6.1.2.1 Physical Examination

A complete physical examination includes patient height, weight, and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system, and additional areas/systems as clinically indicated. Limited physical examination includes vital signs, any change from baseline abnormalities, any new abnormalities, height, weight, and evaluation of patient-reported symptoms.

6.1.2.2 Vital Signs

Vital signs include systolic and diastolic BP, heart rate, respiration rate, and body temperature. For patients receiving antihypertensive medications with either a baseline history of hypertension or new onset of hypertension that develops on study, BP should be monitored per institutional standard practice. Blood pressure assessments will be conducted in triplicate and averaged to determine BP (BP reference Appendix 7).

6.1.2.3 Hematology

Hematology assessments include red blood cell count, hemoglobin, hematocrit, platelet count, and white blood count with differential (absolute counts).

6.1.2.4 Blood Chemistry, Liver Function Tests, and Kidney Function Tests

The blood chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, TBIL, direct bilirubin, ALT, AST, ALP, total protein, and albumin.

Patients with ALT or AST increase should followed up per Table 12.

6.1.2.5 Coagulation

Coagulation tests include PT, INR, and aPTT.

6.1.2.6 Thyroid Function

Thyroid function tests include serum free thyroxine (T4) and thyroid stimulating hormone (TSH).

6.1.2.7 Urinalysis

Urinalysis parameters include urine pH, protein, glucose, and blood; microscopic for white blood cells and red blood cell count. If urinalysis shows ≥ trace protein, then obtain urine P/C. A 24-hour urine sample for quantitative protein should be collected, if possible, for patients with ≥2+ proteinuria.

6.1.2.8 Pregnancy Test

All female patients of childbearing potential must complete a serum pregnancy test at screening and at the safety follow-up visit, and a serum or urine pregnancy test on day 1 of every cycle starting at cycle 2. Serum pregnancy test should be repeated for women with suspected pregnancy. This is not applicable for postmenopausal female patients (ie, no menses for 12 months without an alternative medical cause), and the date of menopause should be recorded instead. Pregnancy testing and contraception are not required for women with documented permanent sterilization (eg, hysterectomy, bilateral salpingectomy and bilateral oophorectomy, or tubal ligation).

6.1.2.9 Electrocardiogram

Standard 12-lead ECGs will be performed after the patient has been resting for 5 to 10 minutes. Electrocardiograms should be performed in triplicate at screening or if single read has a corrected QT interval by Fridericia (QTcF) of ≥480 ms, and whenever feasible. Triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from these 3 ECGs will be averaged to provide a single value for each time point. Eligibility will be based on the average of the triplicate ECG conducted at screening.

6.1.2.10 Echocardiogram

Echocardiogram assessment parameters include shortening fraction and general assessment of cardiac function. MUGAs assessment of left ventricular ejection fraction are permitted if echocardiograms cannot be performed.

6.1.2.11 Knee X-Ray and Knee Magnetic Resonance Imaging

The potential effect of surufatinib on bone development in children and adolescents with growing skeletons will be monitored by knee X-rays and knee MRI if clinically indicated.

6.1.3 Efficacy Assessments

Tumor assessments will be performed at study visits as specified in Table 1.

All measurable and evaluable lesions should be assessed and documented using image-based evaluation. All patients are to be evaluated utilizing contrast-enhanced CT scan of the chest, abdomen, and pelvis, or other acceptable cross-sectional imaging per RECIST version 1.1 (see Appendix 2). Evaluations should include other areas of the body, as clinically indicated. Disease status will be assessed by the Investigator or designated site staff using RECIST version 1.1. The same imaging procedure used to define measurable lesions at baseline must be used throughout the study for each patient, unless medically contraindicated. At the Investigator's discretion, other methods of assessment of measurable disease as per RECIST version 1.1 may be used.

Tumor assessments completed as standard of care prior to signing the informed consent, but within 28 days of first dose of study treatment, may be used as baseline scans.

6.1.4 Pharmacokinetic Evaluations

6.1.4.1 Sampling Collection and Handling

Blood samples will be collected for analysis of surufatinib plasma concentrations in all patients according to the schedule in Table 2. The actual dates and times of PK sampling should be recorded in appropriate eCRF. In addition, the dates and times of the surufatinib dose administered on the day of PK collection and one day before PK collection must be recorded in the eCRF.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided to the sites. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

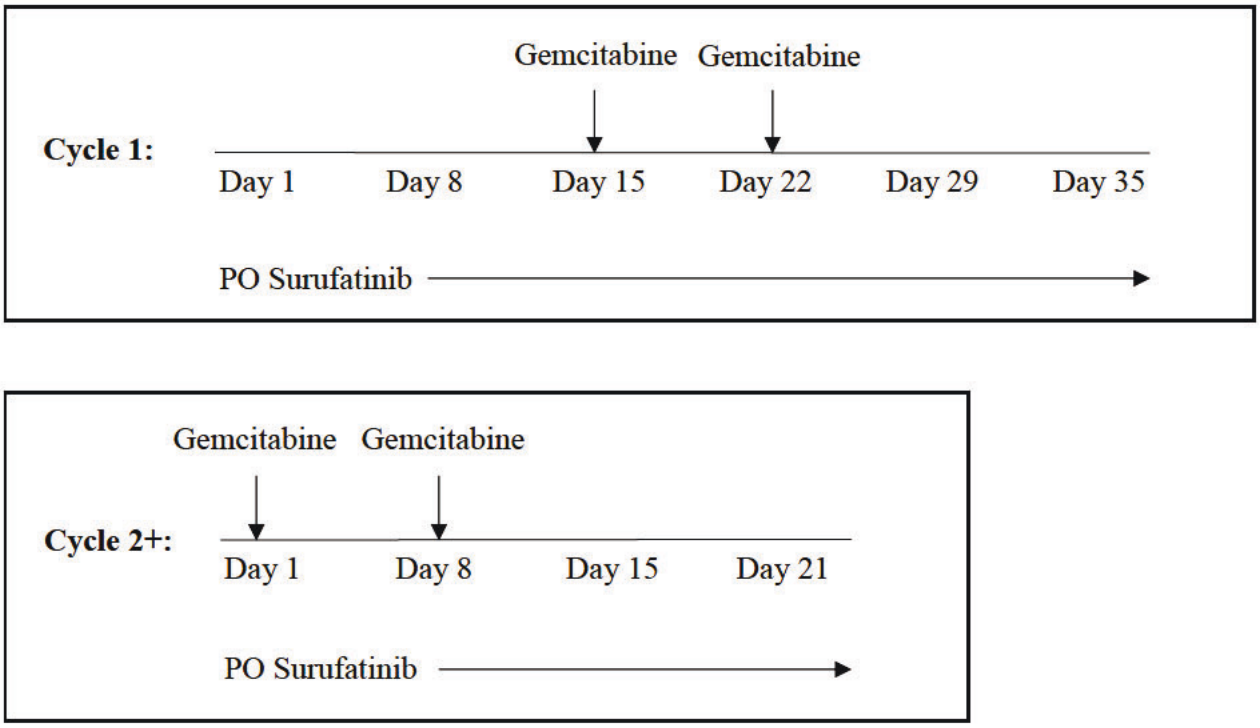
6.1.4.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of surufatinib using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

6.1.5 Treatment Period

Any patient that completes the screening period and meets all eligibility criteria will enter into the treatment period. Patients will be enrolled into a specific dose level or cohort, depending on when they enroll. The DLT evaluation period will last 1 cycle (35 days). Patients who complete the DLT evaluation period may go on to receive up to a total of 17 cycles of therapy as long as they continue to undergo study required assessments and meet criteria to start subsequent cycles.

Figure 3 Dosing Schematic



PO=per os (orally).

Required evaluations can be found in SOE tables in Section 1.2.

Patient may continue subsequent cycles of surufatinib and gemcitabine combination therapy provided that the patient has met the eligibility criteria (with respect to organ function and performance score), has not met any criteria for removal from protocol, and has not experienced a DLT . Patients may continue treatment if the delay from anticipated start of cycle to actual start of cycle is no more than 7 days. Those patients delayed more than 7 days for the start of the subsequent cycle will not be allowed to continue on study.

Criteria to Receive Gemcitabine Mid Cycle:

This applies to patients on the following cycles/days:

- Cycle 1, days 15 and 22
- Cycles 2+, day 8

Patients must have an ANC $\geq 500/mm^3$ AND a platelet count $\geq 50\ 000/mm^3$ to receive gemcitabine midcycle. If a patient does not meet treatment criteria, a CBC/differential count should be rechecked within 3 days. If ANC improves to $\geq 750/mm^3$ and platelets improve to $\geq 50\ 000/mm^3$ within 3 days without intervention, gemcitabine may be given. If gemcitabine cannot be administered within 3 days, gemcitabine is to be held, and appropriate dose modifications are to be followed (DLT definitions are presented in Section 4.2 and dose modifications for toxicity are presented in Section 7.3).

6.1.6 Safety Follow-up

Follow-up on this study is required at 30 days from the last dose of protocol therapy for late onset AEs. The post treatment follow-up will begin when the patient discontinues study treatment and all off-treatment assessments have been completed. Patients should also be asked about concomitant medications at this follow-up. Follow-up data will be submitted per the case report forms (CRFs).

6.1.7 End of Study

A patient will be considered to have completed the study once he or she has completed the last visit or the last scheduled procedure as outlined in Table 1.

The study will be considered completed once the last patient has completed the last visit or last scheduled procedure.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Patients

6.2.1.1 Treatment Interruption

Treatment interruption and resumption parameters are defined in dose modifications Section 7.3.

6.2.1.2 Permanent Discontinuation of Treatment

The Investigator has the right to discontinue a patient from the study for any medical condition that the Investigator determines is in the best interest of the patient, reasons of noncompliance (eg, missed doses and visits), or pregnancy.

Any patient who discontinues treatment should be encouraged to return to the study site for an end of treatment visit and continue with the remaining study visits outlined in Table 1. The primary reason for discontinuation must be recorded on the appropriate eCRF.

Patients will be discontinued from protocol-defined therapy for any of the following reasons:

- Patient determined to be ineligible
  - If the patient was found to be ineligible after starting treatment, follow-up should continue for 30 days from the last administration of study drug or until the toxicity resolves or returns to baseline, whichever is longer unless the patient commences a different anticancer therapy
- Pregnancy or breastfeeding or intent to become pregnant or breastfeed
- Any AE that meets criteria for discontinuation
- Adverse event related to therapy that is Grade ≥3, with the exception of toxicities that do not meet criteria for discontinuation as defined in Section 4.2 describing DLTs
- Dose interruption resulting in an interval between treatments of >21days
- Patient noncompliance that, in the opinion of the Investigator, warrants withdrawal (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent

- Progressive disease, unless in the opinion of the treating physician and agreement from the Sponsor, the patient is clinically benefiting from protocol therapy
- Event (such as concurrent illness, significant drug toxicities, or complications) which, in the opinion of the Investigator, is a contraindication to further dosing or in which discontinuation of the investigational product is judged by the Investigator to be in the best interest of the patient
- Study terminated by sponsor
- Withdrawal of consent or lost to follow-up

Patients who are permanently discontinued from further receipt of protocol treatment, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Patients who are permanently discontinued from receiving protocol treatment because of toxicity will be followed for safety until the toxicities resolve or the completion of the 30-day follow-up period is completed. Patients who are permanently discontinued from receiving protocol treatment because of disease progression will be followed for safety per Section 6.1.6. Exceptions are if consent is withdrawn or the patient is lost to follow-up. Patients who decline to return to the site for evaluations will be offered follow-up by phone as an alternative.

Any patient who permanently discontinues protocol treatment will be removed from protocol.

6.2.1.3 Withdrawal from Study

Patients are at any time free to withdraw from the study, without prejudice to further treatment (withdrawal of parental/guardian consent and/or patient assent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by an investigator and undergo the assessments and procedures scheduled for the post study assessment as in Table 1. Adverse events should be followed up for 30 days after study withdrawal as outlined in Section 8.3.

6.2.1.4 Replacement of Patients

Patients who discontinue their study treatment for any reason other than DLT (eg, early disease progression) during cycle 1 and have not received at least 80% (28 of total 35 doses) of the prescribed oral surufatinib dose and both doses of gemcitabine prior to discontinuation will be replaced with another patient at the same dose level.

6.2.1.5 Patients Lost to Follow-up

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

Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

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

6.3 Study Termination

The Sponsor, ethics committee, or regulatory authorities have the right to stop the study at any time. The reasons for stopping the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

7 STUDY INTERVENTIONS

Study drug interventions are presented in Table 6.

Table 6 Description of Products

Product	Dose	Frequency	Route	Duration
Surufatinib	As per dosing table	QD	Oral	N/A
Gemcitabine	1000 mg/m^2/dose	Cycle 1: Days 15 and 22 Cycles 2+: Days 1 and 8	Intravenous	90 minutes

QD=once daily.

7.1 Surufatinib

7.1.1 Formulation, Storage, Preparation, and Handling

Surufatinib is formulated with CCI [redacted] as CCI [redacted] hard gelatin capsules, in strengths of 25 and 50 mg of surufatinib per capsule. The capsules are packaged in white high-density polyethylene (HDPE) bottles, which should be stored at temperatures between 10° to 30°C (50° to 86°F) and protected from light and moisture. For additional details refer to the IB.

7.1.2 Dosing and Administration

If baseline (predose) PK blood samples need to be collected on the days of PK sample collection, patients must take the investigational product after sampling.

It is recommended that surufatinib capsule(s) be taken with approximately 240 mL water and with a meal. The administration time should be accurately recorded on the day of PK sampling. The dispersed suspensions in water can be prepared from the contents of both 25 and 50 mg capsules for pediatric patients that are unable to swallow the whole capsules. Instructions for administration of surufatinib capsules in suspension are provided in the pharmacy manual.

Palatability is a key characteristic for acceptability of oral drug formulations and compliance, especially in children. The taste and palatability survey will be assessed in patients who have taken surufatinib oral suspension (refer to Appendix 9).

On the day of PK sampling, patients should avoid high-fat, high-calorie meals for the entire day. No caffeine containing foods or drinks, no grapefruit or grapefruit juice, tobacco and tobacco containing products, or alcohol or recreational drugs will be allowed during the PK assessment period (cycle 1).

If vomiting occurs after dosing, the surufatinib dose should not be replaced. If patients miss a dose in the morning, a replacement dose can be taken if it is within 12 hours from the intended missed dose; otherwise, the patient should not make up the missed dose, but resume schedule the following day. The missed dose should be reported to investigators and recorded in the CRF.

Table 7 presents dose to be administered based on patient BSA to achieve the planned dose level (90, 120, 160, or 200 mg/m^2). The table also provides the corresponding dose to be administered if a dose reduction is required for an individual patient (refer to Section 7.3).

Table 7 Surufatinib Dosing Nomogram

90 mg/m2 (Dose Level -1)			
BSA (m^2)	Dose (mg)	Dose Reduction (mg)	% Reduction
0.4-0.64	**50**	25	50%
0.65-0.9	**75**	50	33%
0.91-1.17	**100**	75	25%
1.18-1.36	**125**	75	40%
1.37-1.85	**150**	100	33%
1.86-2.07	**175**	125	29%
≥2.08	**200**	150	25%

120 mg/m2 (Dose Level 1)			
BSA (m^2)	Dose (mg)	Dose Reduction (mg)	% Reduction
0.4-0.64	**75**	50	33%
0.65-0.9	**100**	75	25%
0.91-1.17	**125**	75	40%
1.18-1.36	**150**	100	33%
1.37-1.85	**175**	125	29%
1.86-2.07	**200**	150	25%
≥2.08	**225**	150	33%

160 mg/m2 (Dose Level 2)			
BSA (m^2)	Dose (mg)	Dose Reduction (mg)	% Reduction
0.4-0.64	**100**	75	25%
0.65-0.9	**125**	75	40%
0.91-1.17	**175**	125	29%
1.18-1.36	**200**	150	25%
1.37-1.85	**250**	175	30%
1.86-2.07	**300**	200	33%
≥2.08	**300**	200	33%

200 mg/m2 (Dose Level 3)			
BSA (m^2)	Dose (mg)	Dose Reduction (mg)	% Reduction
0.4-0.64	**125**	75	40%
0.65-0.9	**150**	100	33%
0.91-1.17	**200**	150	25%
1.18-1.36	**250**	175	30%
1.37-1.85	**300**	200	33%
1.86-2.07	**300**	200	33%
≥2.08	**300**	200	33%

BSA=body surface area.
For Spain only: No subjects will be allowed on the study with a BSA ≤0.6 or body weight ≤14 kg.

7.2 Gemcitabine

7.2.1 Formulation, Storage, Preparation, and Handling

Please reference prescription information or pharmacy manual for the detailed information of gemcitabine.

7.2.2 Dosing and Administration

Gemcitabine will be given at a dose of 1000 mg/m^2/dose and infused intravenously over 90 minutes. Additional details regarding preparation and administration are found in the pharmacy manual or package insert.

7.3 Dose Modifications

- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade if the Investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to

Grade 2 during treatment, this will be considered a shift of 1 grade and treated as Grade 1 toxicity for dose modification purposes.

- No dose reductions or interruptions will be required for anemia (non-haemolytic) because it can be satisfactorily managed.
- To recover from acute toxicity, unless otherwise indicated, the treatment can be delayed for up to 14 days. If a treatment delay longer than 14 days is required, the patient should be discontinued from the study treatment.
- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.

Dose modifications apply to surufatinib only, and only 1 dose reduction of surufatinib is permitted (refer to Table 7). Once the dose is reduced, it cannot be increased. There will be no dose modifications for gemcitabine, but the dose of gemcitabine may be held for toxicity.

7.3.1 Dose Modifications for Hematological Toxicity

Dose modifications for hematological toxicity are presented in Table 8.

Table 8 Dose Modifications for Hematological Toxicity

Time Period	Adverse Event	Action
Day 15 or 22 of Cycle 1 **Day 8, Cycles 2+**	Thrombocytopenia Platelets 25 000 – 50 000/mm^3 (**Grade 3**) without clinically significant bleeding	Recheck within 3 days and if improved to ≥50 000/mm^3, administer gemcitabine. If no resolution within 3 days, hold gemcitabine and surufatinib and if improves to ≤Grade 2 within 7 days then resume surufatinib at reduced dose. If patient has already had 1 dose reduction, then protocol therapy should be discontinued.
Day 15 or 22 of Cycle 1 **Day 8, Cycles 2+**	Thrombocytopenia Platelets 25 000 – 50 000/mm^3 (**Grade 3**) with clinically significant bleeding, or Platelets <25 000/mm^3 (**Grade 4**) lasting >7 days or requiring platelet transfusion on 2 separate days within a 7-day period regardless of association with bleeding	Hold gemcitabine and surufatinib and if improves to ≤Grade 2 within 7 days then resume surufatinib at reduced dose. If patient has already had 1 dose reduction, then protocol therapy should be discontinued.
Day 15 or 22 of Cycle 1 **Day 8, Cycles 2+**	Neutropenia ANC <500/mm^3 (**Grade 4**)	Recheck within 3 days and if improved to ≥750/mm^3, administer gemcitabine. If no resolution within 3 days, hold gemcitabine and surufatinib and if improves to ≥750/mm^3 within 7 days then resume surufatinib at reduced dose. Subsequent cycles should be administered with growth factor[1] on day 9 after gemcitabine. If patient has already had 1 dose reduction, then protocol therapy should be discontinued.
Toxicity occurring on days not specified above	Thrombocytopenia Platelets 25 000 – 50 000/mm^3 (**Grade 3**) with clinically significant bleeding, or Platelets <25 000/mm^3 (**Grade 4**) lasting >7 days or requiring platelet transfusion on 2 separate days within a 7-day period regardless of association with bleeding	Hold surufatinib. If improves to ≤Grade 2 within 7 days without intervention, then resume surufatinib at reduced dose. If patient has already had a dose reduction, then protocol therapy should be discontinued.
Toxicity occurring on days not specified above	Neutropenia ANC <500/mm^3 (**Grade 4**)	If persists for >7 days, then hold surufatinib. If improves to ≥750/mm^3 within 7 days, then resume surufatinib at reduced dose. Subsequent cycles should be administered with growth factor on day 9 after gemcitabine. If patient has already had one dose reduction, then protocol therapy should be discontinued.

Table 8 Dose Modifications for Hematological Toxicity

Time Period	Adverse Event	Action
Toxicity occurring on days not specified above	Myelosuppression that causes a delay of >7 day between treatment cycles	Discontinue surufatinib.

[1] Myeloid growth factor support: use of neulasta is not allowed. Granulocyte colony stimulating factor (G-CSF) may be administered at a dose of 5 μg/kg daily beginning on day 23 of cycle 1 or day 9 of cycles 2+ and continuing for a minimum of 7 days and until the post-nadir neutrophil count increases to ≥750/μL.

7.3.2 Dose Modifications for Non-Hematological Toxicity

Dose modifications for non-hematological toxicity are presented in Table 9.

- Patients who have any non-hematological toxicity ≥Grade 3 may continue on protocol therapy if toxicity returns to ≤Grade 1/or baseline within 14 days of drug interruption, and should receive subsequent cycles at a reduced dose as described in Table 7.
- If ≥Grade 3 non-hematological toxicity of same System Organ Class (SOC) recurs after 1 dose reduction, the patient must be removed from protocol therapy.
- Patients who have ≥Grade 3 non-hematological toxicities that does not resolve to ≤Grade 1 or baseline within 7 days after the planned start of the next treatment cycle must be removed from protocol therapy.

Dose modification for specific AEs proteinuria, hypertension, liver toxicities, and hemorrhage are presented in Section 7.3.3.

Table 9 Dose Modifications for Non-Hematological Toxicity

NCI CTCAE Version 5.0 Toxicity Grading	Action	
	Surufatinib	**Gemcitabine**
Grades 1 or 2	None	None
Grade 3		
Expected manageable/reversible with dose reduction	Hold	Hold
Toxicity remains ≥Grade 3 >14 days	Discontinue	Discontinue
Toxicity lasts ≤14 days and resolves to ≤Grade 1 or baseline	Reduce dose if not already reduced	Resume at the same dose
Reoccurrence of Grade 3/4 toxicity of same SOC	Discontinue or discuss with sponsor if the patient is clinically benefiting	Discontinue or discuss with sponsor if the patient is clinically benefiting
Not expected manageable/irreversible with dose reduction	Discontinue	Discontinue
Grade 4 with the exception of febrile neutropenia	Discontinue	Discontinue

CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; SOC=System Organ Class.
Note: Patients who experience gastrointestinal perforation should permanently discontinue study drug.

7.3.3 Dose Modification of Surufatinib for Adverse Events of Special Interest

Dose modification of surufatinib for AEs of special interest (AESI) are provided in Table 10 (proteinuria), Table 11 (hypertension), Table 12 (hepatic disorders), and Table 13 (hemorrhage). AESIs of thyroid dysfunction and acute renal failure should also be monitored.

7.3.3.1 Dose Modifications for Proteinuria

Proteinuria has been reported with surufatinib in adult studies.

- If urinalysis shows ≥2+ protein, then obtain a 24-hour urine sample for protein or a random urine P/C ratio.

Table 10 Dose Modification of Surufatinib for Proteinuria

Grade and Definition	Dose Modification	Suggested Actions
Grade 1: 1+ proteinuria or urinary protein ≥ ULN - <1.0 g/24 hours	None	Follow-up per planned schedule.
Grade 2: Proteinuria 2+ or 3+ or urinary protein 1.0 g to <3.5 g/24 hours or urine P/C 0.5-1.9	None	Provide supportive treatment and increase the frequency of urine monitor to once a week; consult nephrologist if necessary.
Grade 3: Urinary protein ≥3.5 g/24 hours or urine P/C >1.9 (ie, confirmed with a repeat urine P/C within 72 hours)	• Hold surufatinib. • If test results resolve to ≤Grade 2 in less than 14 days, resume surufatinib at reduced dose. • If surufatinib is held ≥14 days, permanently discontinue treatment.	Provide supportive treatment and increase the frequency of urine monitor weekly; consult nephrologist if necessary.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; P/C=protein/creatinine; ULN=upper limit of normal.

Note: The CTCAE grade recorded for proteinuria is to be determined by the urine P/C or 24-hour urine collection; however, the start date of the AE will be recorded as the first instance of proteinuria (ie, urine dipstick). Surufatinib treatment is to be discontinued if a patient develops nephrotic syndrome.

7.3.3.2 Dose Modifications for Hypertension

1. The ULN for BP is defined as a systolic or diastolic BP of 95th percentile for age, height, and gender for pediatric patients. For adolescent, the ULN is 130/80 mmHg. For adult patients (≥18 years in this study), the ULN is 140/90 mmHg.
2. The NCI CTCAE version 5.0 will be used to determine the grade of hypertension for reporting purposes.
3. Elevated BP measurements are to be repeated on the same day to confirm the elevation. If confirmed, patients with elevated BP are to have BP measurements performed at least weekly until BP is < ULN.

Table 11 Dose Modification of Surufatinib for Hypertension

Grade and Definition	Dose Modification and Management
Grade 1: Prehypertension (systolic BP 120 to 139 mmHg or diastolic BP 80 to 89 mmHg) or Pediatric: Systolic/diastolic BP >90th percentile but<95th percentile; Adolescent: BP ≥120/80 even if <95th percentile	None
Grade 2: Stage 1 hypertension (systolic BP 140 to 159 mmHg or diastolic BP 90 to 99 mmHg) if previously within normal range, medical intervention indicated, recurrent or persistent (≥24 hours), symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg , or monotherapy indicated or Pediatric and adolescent: Recurrent or persistent (≥24 hours) BP > ULN; monotherapy indicated; systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; Adolescent: Systolic between 130-139 or diastolic between 80-89 even if <95th percentile	• Initiate antihypertensive therapy if not previously started. • If previously on optimized antihypertensive medical management. • If BP ≥ ULN despite maximal antihypertensive therapy hold surufatinib. o Restart at the same dose if BP returns to < ULN within 14 days of drug interruption after the initiation of an antihypertensive therapy or change in previous antihypertensive therapy. o If the BP remains ≥ ULN after restarting surufatinib then the drug should be held until BP < ULN. If BP returns to < ULN within 14 days of drug interruption, patient may resume surufatinib at a reduced dose. o If the BP remains ≥ ULN for >14 days in any situation, then the patient should be removed from protocol therapy.
Grade 3: Stage 2 hypertension (systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg), medical intervention indicated, >1 drug or more intensive therapy than previously used indicated or Pediatric and adolescent: Systolic and/or diastolic >5 mmHg above the 99th percentile	• Initiate antihypertensive therapy if not previously started. • If previously on optimized antihypertensive medical management hold surufatinib. o If BP returns to < ULN within 14 days of drug interruption, the patient may resume treatment at a reduced dose. o If Grade 3 hypertension reoccurs, despite optimal medical management and a reduced dose of surufatinib, then discontinue surufatinib treatment. o If the BP remains ≥ ULN for >14 days in any situation, then the patient should be removed from protocol therapy.
Grade 4: Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, and hypertensive crisis) or urgent intervention indicated	Discontinue surufatinib treatment.

BP=blood pressure; ULN=upper limit of normal.

7.3.3.3 Dose Modifications for Hepatic Disorders

Table 12 Dose Modification of Surufatinib for Hepatic Disorders

Grade and Definition	Dose Adjustment	Suggested Actions
Grade 1: ALT >1 to 3×ULN or AST >1 to 3×ULN	None	Follow-up per planned schedule.
Grade 2: ALT >3 to 5×ULN or AST >3 to 5×ULN	Maintain the original dose, provide supportive care of complications of liver impairment, and observation for 1 week.	Follow-up per planned schedule. Discontinue study drug(s) if the biochemical criteria for Hy's Law have been met.[1]
Grade 3: ALT >5 to 10×ULN or AST >5 to 10×ULN and bilirubin ≤ ULN	○ Continue surufatinib for 7 days ○ If ALT/AST improves to ≤5×ULN within 7 days, continue surufatinib at the same dose; ○ If ALT/AST remains >5 to 10×ULN hold surufatinib for up to 14 days; ○ If ALT/AST resolves or improves to ≤Grade 1/baseline between 8 and <21 days, resume surufatinib at a reduce dose (if possible); ○ If dose reduction not possible discontinue protocol therapy or discuss with sponsor if the patient is clinically benefiting.	Provide supportive care and increase the frequency of liver function monitoring to twice a week; consult expert if necessary. Evaluate the biochemical criteria for Hy's Law.[1]
Grade 3: ALT >10 to 20×ULN or AST >10 to 20×ULN and bilirubin ≤ ULN	○ Hold surufatinib ○ If resolves or improves to ≤Grade 1/baseline within 7 days, resume surufatinib at a reduced dose; ○ If dose reduction not possible discontinue protocol therapy or discuss with sponsor if the patient is clinically benefiting.	Provide supportive care and increase the frequency of liver function monitoring to twice a week; consult expert if necessary. Evaluate the biochemical criteria for Hy's Law.[1]
Grade 4: ALT >20×ULN or AST >20×ULN	Discontinue surufatinib.	Urgent medical intervention indicated. Discontinue study drug(s) if the biochemical criteria for Hy's Law have been met.[1]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.
[1] See Appendix 6 for important additional information.
[2] For the study sites in the US, ALT ULN=45 U/L, AST ULN=50 U/L as referenced in Appendix 8.

7.3.3.4 Dose Modifications for Hemorrhage

Table 13 Dose Modification of Surufatinib for Hemorrhage

Grade and Definition	Dose Modification	Suggested Actions
Grade 1	None	Follow-up per planned schedule.
Intolerable **Grade 2**	Hold surufatinib treatment. Resume at a reduced dose if resolves to ≤Grade 1 within 21 days. Discontinue if lasting >21 days	Active management.
≥Grade 3	Discontinue surufatinib.	Immediate medical intervention to identify and treat the source of bleeding.

7.3.3.5 Dose Modifications for Thyroid Toxicity

Thyroid toxicity will be handled like any other non-hematological toxicity. Patients with Grade 2 hypothyroidism adequately managed with thyroid hormone replacement may continue on protocol therapy.

7.3.4 Dose Modifications for Diarrhea

An anti-diarrheal agent may be prescribed at the onset of diarrhea and the patient should be instructed and education to initiate anti-diarrheal treatment with the onset of diarrhea.

7.3.5 Dose Modifications for Thromboembolic Events

If a thromboembolic event is confirmed, surufatinib should be held until therapeutic anticoagulation with heparins is established. Surufatinib may be resumed at the same dose level in patients who are stable and have uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) and are deriving clinical benefit.

7.4 Assessment and Verification of Compliance

Records of treatment compliance for each patient will be kept during the study. Clinical research associates will review treatment compliance during site visits and at the completion of study. Compliance will be monitored using the patient diary as well as the electronic medical record documentation of oral compliance with surufatinib, IV compliance with gemcitabine, and study assessment compliance.

7.5 Prior and Concomitant Therapies

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the CRF. If medically feasible, patients taking regular medication(s) should be maintained on this medications(s) throughout the study period.

7.5.1 Prohibited Therapies

Concurrent anticancer therapy, including chemotherapy, radiation therapy, immunotherapy, immunomodulating agents (with the exception of corticosteroids), or biologic therapy may not be administered to patients receiving study treatment. If these treatments are administered the patient will be removed from protocol therapy. Patients may not be on clozapine, natalizumab, leflunomide, tofacitinib, or warfarin as these may interact with gemcitabine.

7.5.2 Permitted Therapies

Granulocyte colony stimulating factors should not be used prophylactically during the DLT evaluation period (cycle 1). Use of prophylactic colony stimulating factors may be considered after cycle 1 if there is sustained myelosuppression in cycle 1 and after discussion with the PI.

Patients may receive treatment with corticosteroids (for nausea/emesis).

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen and diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

Supportive care and other medications that are considered necessary for the patient's well-being, may be given at the discretion of the Investigator. This may include (but is not limited to) antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care.

7.5.3 Drug-Drug Interactions

In vitro metabolism data indicate that CYP3A plays an important role in the metabolism of surufatinib. The potential effects of medications that can affect the PK of surufatinib via the CYP3A pathway have not been tested in the clinic. Therefore, medications that are strong/moderate inhibitors or strong/moderate inducers of CYP3A are prohibited and should not be administered 2 weeks or 5 half-lives (3 weeks for St John's wort) before the study or concomitantly with surufatinib during the course of the study. Examples of these medications are listed in Appendix 4.

In vitro, surufatinib is shown to have the potential to inhibit CYP3A, P-gp, and breast cancer resistance protein (BCRP) (refer to the IB). Patients should avoid concomitant use of medications that are sensitive substrates or substrates with narrow therapeutic windows of CYP3A, P-gp, or BCRP where possible. If used together, patients should be monitored more frequently for adverse reactions (ARs), and consider dose reduction of the CYP3A, P-gp, or BCRP substrate medication should occur. Examples of the medications that are sensitive substrates and substrates with narrow therapeutic windows of CYP3A, P-gp, and BCRP are listed in Appendix 4.

7.6 Drug Accountability

All study drugs required for this study will be provided by HUTCHMED or a contract research organization (CRO). The recipient will acknowledge receipt of the study drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to, and disposed by the study site should be recorded by using the Drug Inventory Log.

Study drug will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to HUTCHMED or designated CRO with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

8 SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All AEs will be assessed according to the NCI CTCAE version 5.0 for severity or intensity.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory findings), symptom, or disease (new or exacerbated) temporally associated with the use of a study medication.

Any deterioration due to disease under study and associated symptoms or findings should not be regarded as an AE as long as the deterioration is clearly due to disease and can be anticipated.

AE examples include, but are not limited to:

a. Exacerbation of a chronic or intermittent pre-existing condition including either an increased in frequency and/or intensity of the condition.
b. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without AE."
c. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator.
d. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
e. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
f. Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event.

An AE does not include:

a. Medical or surgical procedures (eg, pre-scheduled surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an AE.
b. Anticipated day to day fluctuations of preexisting disease(s) or condition(s) presented or detected prior to or at the start of investigational therapy that do not worsen.
c. Situations in which an untoward medical occurrence (eg, hospitalization for an elective surgery, social, and/or convenience admissions).

The term AE is used generally to include any AE whether serious or non-serious.

8.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose during any study phase (ie, run-in, treatment, washout, follow-up), that results in any of the following outcomes:

- Death
- Immediately life-threatening situation (patient is at immediate risk of death at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital abnormality or birth defect in the offspring of a patient
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when based upon appropriate medical judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

8.1.3 Causality or Relatedness

The Investigator is required to provide an assessment of relationship of an AE and SAE to surufatinib and/or gemcitabine. A number of factors should be considered in making this assessment including:

a. The temporal relationship of the event to the administration of study drugs
b. Whether an alternative etiology has been identified
c. Biological plausibility
d. Dechallenge (Positive dechallenge is a response observed for the reduction or disappearance of adverse drug reactions on withdrawal of a drug from a patient.)
e. Rechallenge (Positive rechallenge: If the patient showed return of adverse effects after restart of a drug.)

The Investigator will assess causal relationship between investigational product and each AE, and answer “yes” or “no” to the question: ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

The relationship to study drugs should be assessed using the following definitions:

a. Not related: A clear-cut alternative explanation exists that the AE has an etiology other than study drugs (eg, preexisting condition, underlying disease, inter-current illness, or concomitant medication).
b. Related: There is a reasonable possibility that the product caused the treatment under investigation. In this definition, the phrase “a reasonable possibility” means that the relationship to study treatment cannot be ruled out.
c. Adverse reaction (AR): An AR is any AE caused by a drug.

d. Suspected adverse reaction (SAR): An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.
e. Unexpected: An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.
f. Gemcitabine has been approved for marketing in the US and in the EU/UK. The health authority approved prescription drug labeling is used as the basis for determining whether an event is unexpected for reporting purposes.

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.2 Adverse Events of Gemcitabine

Toxicity profile of gemcitabine from package insert:

Common (>20% of patients)

Alopecia, rash maculopapular, constipation, diarrhea, nausea, vomiting, anemia, white blood cell decreased, neutrophil count decreased, platelet count decreased, ALP increased, ALT increased, AST increased, bilirubin increased, infection1, peripheral motor neuropathy, peripheral sensory neuropathy, paresthesia, hematuria, proteinuria, dyspnea, fatigue, fever, pain
Occasional (5% to 20% of patients)

Edema limbs, localized edema, hypotension, hyperglycemia, hypocalcemia, hypomagnesemia, anorexia, mucositis oral, pharyngeal mucositis, hemorrhage, bone pain, headache, somnolence, psychiatric disorders – other: mood disorders, serum creatinine increased, investigations – other: increased blood urea nitrogen, flu-like syndrome
Rare (<5% of patients)

Cardiac disorders, other: arrhythmias, heart failure, myocardial infarction, vasculitis, bullous dermatitis, skin infection, infusion site reaction, radiation recall reaction, febrile neutropenia, hepatic failure, hepatobiliary disorders – other: sinusoidal obstruction syndrome, anaphylaxis, hearing impaired, arthralgia, myalgia, hemolytic uremic syndrome, AKI, blood and lymphatic system disorders – other: thrombotic microangiopathy, adult respiratory distress syndrome, bronchospasm, respiratory, thoracic and mediastinal disorders – other: interstitial lung disease, pulmonary edema, pulmonary fibrosis, respiratory failure
Pregnancy/Lactation

Pregnancy Category D
Gemcitabine is embryotoxic causing fetal malformations (cleft palate and incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery and absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended

human dose on a mg/m^2 basis). In mice, embryolethality was observed following doses of 0.25 mg/kg/day (approximately 1/1300 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. It is not known whether gemcitabine or its metabolites are excreted in human milk.

8.3 Documenting Adverse Events

Adverse events will be collected throughout the study, from informed consent until 30 days after the last dose of protocol therapy (follow-up period). The follow-up period is defined as 30 days after study treatment is discontinued. SAEs occurring in the follow-up period should be reported to the regulatory authorities and Sponsor as delineated in Section 8.4.

8.3.1 Timeframe for Collection

Adverse events will be documented from the time of study enrollment through 30 days after the last day of study treatment.

All AEs (irrespective of suspected causality) and SAEs must be followed until one of the following occurs:

- Resolved or improved to baseline
- Death
- Start of new anticancer medication
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

8.4 Reporting Adverse Events

8.4.1 Expedited Reporting Period

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The Investigator must report such events (both initial and follow-up) to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event.

Serious adverse events (from informed consent to 30 days following the last dose of study treatment or initiating a new anti-tumor therapy) must report to the Sponsor within 24 hours after first learning of the event, regardless of relationship to study treatment.

8.4.2 All Serious Adverse Events and Protocol-Defined Adverse Events of Special Interest

Investigators will submit reports of all SAEs and protocol-defined events of special interest, regardless of attribution, to the Sponsor or the Sponsor's designee via fax or email within 24 hours of learning of the events.

For initial SAEs and protocol-defined events of special interest reports, investigators should record all case details that can be gathered within 24 hours on a SAE reporting form. Relevant follow-up information should be submitted to the Sponsor or the Sponsor's designee as soon as it becomes available and/or upon request within 24 hours of the Investigator's awareness of the events.

Investigators must also comply with local requirements for reporting SAEs to the local health authority and Independent Ethics Committee/Institutional Review Board (IEC/IRB).

8.4.2.1 Drug-Induced Liver Injury

Report all potential events of drug-induced liver injury (DILI), as defined below, regardless of whether it is a non-serious or serious AE to the Sponsor no more than 24 hours after learning of the event.

- Serum AST or ALT >3 × ULN together with TBIL >2 × ULN.

This combination of lab abnormalities meets the biochemical criteria for Hy's Law, which is associated with a markedly increased possibility of severe DILI, and may progress to liver transplantation or death. Some patients may present with symptoms such as: fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). If the biochemical criteria for Hy's Law is met, surufatinib should be immediately discontinued, and patients need to be very closely monitored (bilirubin, ALP, AST, ALT measured 2 to 3 times weekly until the results return to baseline or normal), and other causes of liver injury evaluated (eg, new or worsening hepatobiliary metastases; non-malignant biliary obstruction; viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis; preexisting or acute liver disease; ischemic liver injury; right-sided congestive heart failure; new or worsening liver metastases; or concomitant medication that could cause the observed injury). Consultation with a gastroenterologist or hepatologist should be considered.

The findings described above must be reported to the Sponsor no more than 24 hours after awareness of the event.

8.4.2.2 Severe Hemorrhagic Events

When a hemorrhagic event meets NCI CTCAE ≥Grade 3 severity (regardless of whether it is serious or non-serious), the event should be reported to the Sponsor no more than 24 hours after first awareness of the event.

8.5 Adverse Events of Special Interest for Surufatinib

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. AESI for surufatinib include:

- Hepatic disorders
- Proteinuria
- Hypertension
- Thyroid dysfunction
- Hemorrhage
- Acute renal failure

8.6 Clinical Laboratory Findings

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (eg, abnormalities that require study drug dose

modification, discontinuation of study drug, more frequent follow-up assessments, or further diagnostic investigation).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded on the AE/SAE eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mmol/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

8.7 Pregnancy

If a patient becomes pregnant during the course of the study, protocol therapy should be discontinued immediately.

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be reported to the PI as well as the Sponsor using the appropriate forms and within 24 hours of knowledge of the event.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient was withdrawn from the study.

If a pregnancy occurs during exposure to protocol therapy or in the 30 days after discontinuing investigational product, then investigators or other site personnel must inform the PI and the appropriate Sponsor representatives immediately, or **no later than 24 hours** of when he/she becomes aware of it.

The same timelines apply when outcome information is available.

8.8 Overdose or Misuse

There are no data on overdose in pediatrics since this is a first in pediatrics study of surufatinib alone or in combination with gemcitabine. There is no definition of what constitutes an overdose. There is no known antidote.

Investigators should be advised that any patient who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.
- An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then investigators or other site personnel must inform the PI and the Sponsor representatives **within 24 hours** of when he/she becomes aware of it.

9 STATISTICAL ANALYSIS

All statistical analysis will be performed under the direction of the Sponsor's personnel. Details of the statistical analysis and data reporting will be provided in the Statistical Analysis Plan (SAP) document finalized prior to database lock.

The timing of analysis for each cohort may be different depending on completion of each cohort, and the final analysis of the study will be conducted at the time of the analysis of the last cohort.

9.1 Hypothesis

No formal hypothesis testing is planned for the study.

9.2 Population

9.2.1 Sample Size Rationale

Up to 36 patients are to be enrolled in this study Three dose escalation levels will be explored using the rolling 6 design which will lead to maximum 18 evaluable patients. There is 1 additional dose level for dose de-escalation if starting dose is not tolerable. Then, up to 12 evaluable patients will be evaluated in the PK expansion cohort. Assuming a 15% unevaluable rate with respect to the DLT evaluation for dose escalation portion or PK assessment for PK expansion cohort, it is expected to have up to 36 patients in total for this study.

9.2.2 Analysis Populations

The following populations will be defined for this study:

- **DLT Evaluable Set** (dose escalation phase): This population includes all patients enrolled in the dose escalation phase of the study who receive at least 80% (28 of 35 doses) of the prescribed oral surufatinib dose and both doses of gemcitabine during the DLT evaluation period or who discontinued treatment due to a DLT.
- **Safety Analysis Set** (All Treated Population): This population includes all patients who have received at least 1 dose of surufatinib or gemcitabine. Safety and efficacy data will be evaluated based on this population's outcome. Patients in the safety analysis set will be analyzed by their actual dose initially received. If patients have dose reduction during the study, all data will be summarized/analyzed based on the initial dose of study treatment received.
- **Pharmacokinetic Analysis Set**: This population will include all patients who received at least 1 dose of surufatinib and have at least one PK sample obtained and analyzed.

9.3 Statistical Analysis Methods

Data will be summarized by dose cohorts using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and PK measurements. Time to event variables will be summarized descriptively using the Kaplan-Meier (KM) method. The quartiles including median along with 80% and 95% CIs will be reported using the Brookmeyer and Crowley method (using the log-log transformation for CI) (Brookmeyer 1982). Exact CIs for binomial proportions will be derived using the Clopper-Pearson method (Clopper 1934). Analyses will be performed using SAS® (version 9.1 or higher).

9.3.1 Disposition

The number and percentage of patients who were enrolled in the study, treated, discontinued from study treatment (s), and discontinued from study will be presented for all enrolled patients. The primary reason for treatment discontinuation and study discontinuation will be summarized according to the categories in the eCRF. Important protocol deviations will be summarized and listed by category.

9.3.2 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the safety analysis set using descriptive statistics. A summary of baseline patient and disease characteristics, diagnosis, medical history, and prior therapies will be reported using descriptive statistics.

Other patient characteristics will be summarized as deemed appropriate.

9.3.3 Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study treatment (s). Concomitant medications will be defined as medications that 1) started before the first dose of study treatment (s) and were continuing at the time of the first dose of study treatment (s), or 2) started on or after the date of the first dose of study treatment (s) up to 30 days after the last treatment. Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes and will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. A listing of prior and concomitant medications will be provided.

9.3.4 Efficacy Analyses

9.3.4.1 Objective Response Rate

Objective response rate is defined as the proportion of patients with a BOR of CR or PR as determined by the Investigator using RECIST version 1.1. BOR is defined as the best response recorded from the start of study drug (s) until documented RECIST version 1.1 progression or the start date of new anticancer therapy, whichever comes first. Both confirmed and unconfirmed responses will be evaluated. To be assigned a status of confirmed PR or CR, the response must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

The ORR and the corresponding 2--sided Clopper-Pearson 80% CI will be presented.

9.3.4.2 Duration of Response

Duration of response is defined as the time from the first occurrence of PR or CR, whichever comes first until disease progression or death. Duration of response will be summarized separately for both confirmed and unconfirmed responders using Kaplan-Meier methodology.

9.3.4.3 Disease Control Rate

Disease control rate is defined as the proportion of patients with a BOR of CR, PR, or SD as determined by the Investigator using RECIST version 1.1. The DCR and the corresponding 2--sided Clopper-Pearson 80% CI will be presented.

9.3.4.4 Time to Response

Time to response is defined as the time (months) from start of study drug until the date of first occurrence of PR or CR. Time to response will be summarized for responders using Kaplan-Meier methodology.

9.3.4.5 Progression-Free Survival

Progression-free Survival is defined as the time (months) from the start of study treatment (s) until the first radiographic documentation of objective progression as assessed by the investigator using RECIST Version 1.1 or death from any cause. PFS assessed by the investigators per RECIST v1.1 will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimates of PFS will be plotted over time. The corresponding quartiles (including the median), if estimable, will also be estimated using Kaplan-Meier method. Two-sided 95% CIs of median, if estimable, will be constructed with generalized Brookmeyer and Crowley method (Brookmeyer 1982).

9.3.5 Safety Analysis

The summary of the exposure to study treatments (surufatinib and gemcitabine), AEs including DLTs, AEs leading to drug modification or discontinuation, changes in laboratory results, changes in vital signs, etc, will be presented.

The severity of all AEs will be graded according to NCI CTCAE version 5.0, and the AE verbatim term will be coded by the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs are defined as AEs that started or worsened in severity on or after the first dose of study drug and no later than 30 days after the date of last study drug administration.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings. The number and frequency of patients experiencing AEs will be summarized according to SOC and preferred term (PT). If a patient reports a TEAE more than once within that SOC/PT, the AE with the highest severity will be used in the corresponding severity summaries.

The following safety summaries will be produced:

- Overview of AEs
- Summary of DLTs
- Summary of DLT-equivalent (DLTs which occur outside the DLT evaluation window)
- Summary of TEAEs, including severity and relationship to study drug
- Summary of AESIs for surufatinib, including severity and relationship to study drug
- Summary of serious TEAEs
- Summary of TEAEs leading to dose interruption, dose reduction, or termination of study drug

The above summaries will be repeated for TEAEs related to study drug.

Drug exposure, including number of cycles received, total duration of exposure, cumulative dose received (mg), dose intensity, and relative dose intensity of surufatinib and gemcitabine will be summarized. The number and percentage of patients requiring dose interruption, dose delay, dose reduction, and treatment discontinuation because of AEs will be summarized. The reasons for dose modifications will also be summarized for each drug.

For laboratory tests that are graded by NCI CTCAE version 5.0 or higher, results will be summarized by grade. Treatment-emergent changes as defined by worsening of at least one grade from baseline will be summarized by the maximum post-baseline grade. A shift-table summarizing shifts from baseline to maximum post-baseline grade will be presented.

The changes in vital signs and ECOG PS scores from baseline will be summarized. Changes in 12-lead ECG (eg, changes in QTcF) will be summarized.

9.3.6 Other Analysis

9.3.6.1 Taste and Palatability Survey

Data for the evaluation of taste of surufatinib oral suspension will be summarized on a scale of 1 (very bad) through 5 (very nice) .

9.3.7 Pharmacokinetics Analysis

Evaluation on PK will be performed on the PK analysis set. Concentration data of surufatinib in plasma will be tabulated and summarized using descriptive statistics (number of patients [n]; arithmetic mean with standard deviation; coefficient of variation [CV]; and median, minimum, and maximum) as appropriate.

PK parameters of surufatinib to be determined using a noncompartmental approach include, but are not limited to C_{max}, effective $T_{1/2}$, time to reach the maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC), minimum plasma concentration (C_{min}), apparent total clearance from plasma after oral administration (CL/F) at steady state, and accumulation ratio. Additional PK parameters may be included if deemed appropriate. PK analysis will be performed using actual blood collection times relative to dosing times recorded in the raw data. If an actual blood collection time or a dosing time is missing, the nominal time may be used. Details of the PK analysis, including data handling rules and software used to perform the PK analysis, will be provided in the PK SAP.

9.4 Timing of Analyses

Safety and PK data will be reviewed by dose level during the dose escalation phase of the study. The purpose of these reviews is to evaluate safety and tolerability for each dose escalation and determine if a DLT has been observed.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, consensus, and ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH GCP guidelines, and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The IEC/IRB must review the protocol and amendments, IB, ICF, study-relevant materials (such as advertisements for patient recruitment), and any other essential documents. IEC/IRB approval is to be obtained prior to the start of the study at the Investigator's site.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. All SAEs or other significant safety findings should be reported to the Sponsor, the IEC/IRB, and applicable regulatory authorities as required. During the study, protocol deviations that may increase a patient's risk should be reported to the IEC/IRB in a timely manner.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB
- Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC/IRB, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.3 Data Privacy

All information about the study drug (such as patent application, formulation, manufacturing process, and basic study information) is considered confidential as long as it is unpublished.

All information obtained in the study is considered confidential. The Sponsor will open the information to investigational personnel and any other regulatory authority when necessary. To ensure the completeness of the study analysis data, investigational personnel are accountable for providing all results and data to the Sponsor.

Investigators must guarantee the privacy of patients by not disclosing patient-related information to third parties without authorization. eCRFs and other documents submitted to the Sponsor should not contain the patient's name.

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.
- Patients are identified only by unique identifier. Investigators may retain the identification forms, which include patient numbers, names, and addresses. Informed consent forms and other documents should be documented properly and should not be given to the Sponsor.
- The patient must be informed that his or her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for his or her data to be used as described in the informed consent.
- The patient must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

10.4 Disclosure

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

10.5 Data Quality Assurance

- To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study.
- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IEC/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).

10.6 Informed Consent

- Investigators or designees must obtain the signed ICF from patients prior to conducting any study-related procedures.

- The Investigator or his/her representative will explain the nature of the study to the participant or to their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IEC/IRB or study site.
- Patients must be informed that they may withdraw consent to participate in the study without any limitations. If the patient cannot sign the ICF, a legally acceptable representative of the patient must sign the ICF.
- If the patient and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the patient and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the patient and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.
- Informed consent should be recorded on the eCRF.
- If the benefit/risk assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to patients (including patients who have already received the study drug).
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

11 OVERSIGHT

11.1 Safety Review Committee

The SRC will be established under a charter to conduct safety data reviews during the study. The SRC will be comprised of sponsor and CRO medical team members and the site investigators. The SRC will determine whether it is safe to continue to the next predefined dose level, stay at the currently assigned dose level, or whether the dose should be de-escalated to a lower dose level and finally to determine the MTD/RP2D.

11.2 Quality Control and Assurance

The clinical study will be executed and reported following GCPs, all applicable regulatory requirements and applicable standard operating procedures, including quality control of documents.

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site. The Sponsor and Investigator will ensure that any individual or party who performs study-related duties or functions on behalf of the Sponsor/Investigator is qualified to perform the study-related duties or functions.

The overall procedures for quality assurance of clinical study data are described in the Sponsor or designee's standard operational procedures. The planned quality assurance and quality control procedures for the study are described in the following sections.

11.2.1 Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the Sponsor's personnel (or designated CRO) will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence of the protocol to GCP, and the progress of enrollment and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel including the Investigator must be available to assist the field monitor during these visits.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The Sponsor's monitoring standards require full verification of the informed consent, adherence to the inclusion/exclusion criteria, and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

11.2.2 Audits

Authorized representatives of the Sponsor, a regulatory/competent authority, and/or an IEC/IRB representative may visit the site to perform audits or inspections, including source data verification. Should this occur, the Investigator is responsible for the following:

- Informing the Sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the Sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit

- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection
- Documents patient to audit or inspection including but not limited to all source documents, CRFs, medical records, correspondence, ICFs, IEC/IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also patient to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the Investigator's institution.

In all instances, the confidentiality of the data must be respected.

11.2.3 Records

11.2.3.1 Data Capture and Management

The term eCRF refers to the electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all patients, including screen failures, data will be collected on source documents first. The PI is responsible for assuring that the data entered into eCRFs is complete and accurate and that entry and updates are performed in a timely manner. Data will be collected at the study sites, and the data will be transmitted to a designated CRO for centralized analysis, as well as for further processing and data reconciliation. Imaging data will be collected at the study sites, and a designated CRO will perform further processing, data reconciliation, and holding.

At all times, the PI has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the EDC. Patient source documents are the Investigator's/physician's patient records maintained at the study site. In cases where the source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts.

The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

11.2.3.2 Source Documentation

- The Investigator/institution should maintain accurate source documents and study records for all patients that support the information entered in the eCRF.
- Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry.
- All information recorded on eCRFs must be traceable to source documents in the patient's file. Any changes should be explained if necessary (eg, via an audit trail).

11.2.3.3 Records Retention

Records and documents, including signed ICFs, source documents, study drug documents, monitoring visit records, regulatory documents, and all other correspondence and documents pertaining to the conduct of this study must be retained by the Investigator for at least 5 years after study completion, unless local regulations or institutional policies require a longer retention period.

If the documents cannot be stored properly at the investigational site, the documents can be transferred by the Investigator and sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. No records may be transferred to another location or party without written notification to the sponsor.

No records may be destroyed during the retention period following study completion or discontinuation without the written approval of the Sponsor. Records must be destroyed in a manner that ensures confidentiality.

11.3 Study Termination or Study Site Closure

The Sponsor and the Investigator have the right to close out a study site prematurely.

Investigator's Decision

The Investigator must notify the Sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the Investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The Investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The Investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IEC/IRB, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

12 PUBLICATION POLICY

The study results may be published in scientific journals. The names of investigators who make an important contribution to the study implementation and management and personnel who make an important contribution to the study design, analysis, and interpretation (such as the Sponsor's staff or consultants) will be listed in the publication. The Sponsor will provide the article to investigators for review prior to publishing any study results. Investigators must obtain approval from the Sponsor before contributing to any related articles or abstracts.

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

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

13 FINANCING AND INSURANCE

Financing and insurance information will be addressed in a separate agreement.

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15 APPENDICES

APPENDIX 1 KARNOFSKY/LANSKEY PERFORMANCE STATUS SCALE

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	**100**	Fully active
90	Able to carry on normal activity	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	**60**	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	**40**	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	**20**	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	**10**	Completely disabled, not even passive play

APPENDIX 2 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST VERSION 1.1)

Selected sections from the RECIST version 1.1, are presented below.

1. Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

1.1.1 Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1.2 Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥10 but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI scan can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT scan is preferred over chest X-ray, particularly when progression is an important endpoint, since CT scan is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT scan slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT scan or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT scan is done, the decision as to whether non-contrast CT scan or MRI (enhanced or non-enhanced) will be

performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

2. Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least 1 measurable lesion, as detailed above.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only 1 or 2 organ sites involved, a maximum of 2 lesions (1 site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to characterize further any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the electronic Case Report Form (eCRF) (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3 Response Criteria

2.3.1 Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study.

2.3.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be 0 even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (BML is equivalent to a "less than" sign.) (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size

when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

2.3.3 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits.
- PD: Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

2.3.4 Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion).

Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

^{18}F-Fluorodeoxyglucose Positron Emission Tomography

While ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly, possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

A negative FDG-PET scan at baseline with a positive FDG-PET scan during the study is a sign of PD based on a new lesion.

In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

- If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT scan, this will be considered PD.
- If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT scan, additional follow-up CT scans are needed to determine whether there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT scan that is not progressing on the basis of the anatomic images, this will not be considered PD.

2.4 Evaluation of Response

2.4.1 Time Point Response (Overall Response)

It is assumed that at each protocol specified time point, a response assessment occurs. Table 14 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only Table 15 is to be used.

Table 14 Time Point Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

Table 15 Time Point Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

2.4.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is NE at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and, during the study, only 2 lesions were assessed, but

those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is NE. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being NE at that time point.

2.4.3 Best Overall Response: All Time Points

The BOR is determined once all the data for the patient is known. Best response determination in studies where confirmation of CR or PR is not required: Best response in these studies is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second, and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered NE.

Best response determination in studies where confirmation of CR or PR is required: Complete response or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in Table 16.

Table 16 Best Overall Response When Confirmation of Complete Response and Partial Response is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE

NE	NE	NE

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, and NE=not evaluable.
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 14 and Table 15.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (ie, primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

2.5 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6 to 8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (eg, time to progression, disease-free survival, PFS) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized

comparative studies in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6 to 8 weeks on treatment or every 3 to 4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory Measurement/Duration of Response

2.6.1. Confirmation

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies (see the paper by Bogaerts et al. in this Special Issue 10). However, in all other circumstances, for example in randomized studies (phase 2 or 3) or in studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

2.6.2. Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The DoR and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

APPENDIX 3 SURUFATINIB DOSING NOMOGRAM

Surufatinib Dosing Nomogram

90 mg/m² (Dose Level -1)			
BSA (m²)	**Dose (mg)**	**Dose Reduction (mg)**	**% Reduction**
0.4-0.64	**50**	25	50%
0.65-0.9	**75**	50	33%
0.91-1.17	**100**	75	25%
1.18-1.36	**125**	75	40%
1.37-1.85	**150**	100	33%
1.86-2.07	**175**	125	29%
≥2.08	**200**	150	25%

120 mg/m² (Dose Level 1)			
BSA (m²)	**Dose (mg)**	**Dose Reduction (mg)**	**% Reduction**
0.4-0.64	**75**	50	33%
0.65-0.9	**100**	75	25%
0.91-1.17	**125**	75	40%
1.18-1.36	**150**	100	33%
1.37-1.85	**175**	125	29%
1.86-2.07	**200**	150	25%
≥2.08	**225**	150	33%

160 mg/m² (Dose Level 2)			
BSA (m²)	**Dose (mg)**	**Dose Reduction (mg)**	**% Reduction**
0.4-0.64	**100**	75	25%
0.65-0.9	**125**	75	40%
0.91-1.17	**175**	125	29%
1.18-1.36	**200**	150	25%
1.37-1.85	**250**	175	30%
1.86-2.07	**300**	200	33%
≥2.08	**300**	200	33%

200 mg/m² (Dose Level 3)			
BSA (m²)	**Dose (mg)**	**Dose Reduction (mg)**	**% Reduction**
0.4-0.64	**125**	75	40%
0.65-0.9	**150**	100	33%
0.91-1.17	**200**	150	25%
1.18-1.36	**250**	175	30%
1.37-1.85	**300**	200	33%
1.86-2.07	**300**	200	33%
≥2.08	**300**	200	33%

BSA=body surface area.
For Spain only: No subjects will be allowed on the study with a BSA ≤0.6 or body weight ≤14 kg.
Note: This table also appears in main text as Table 7.

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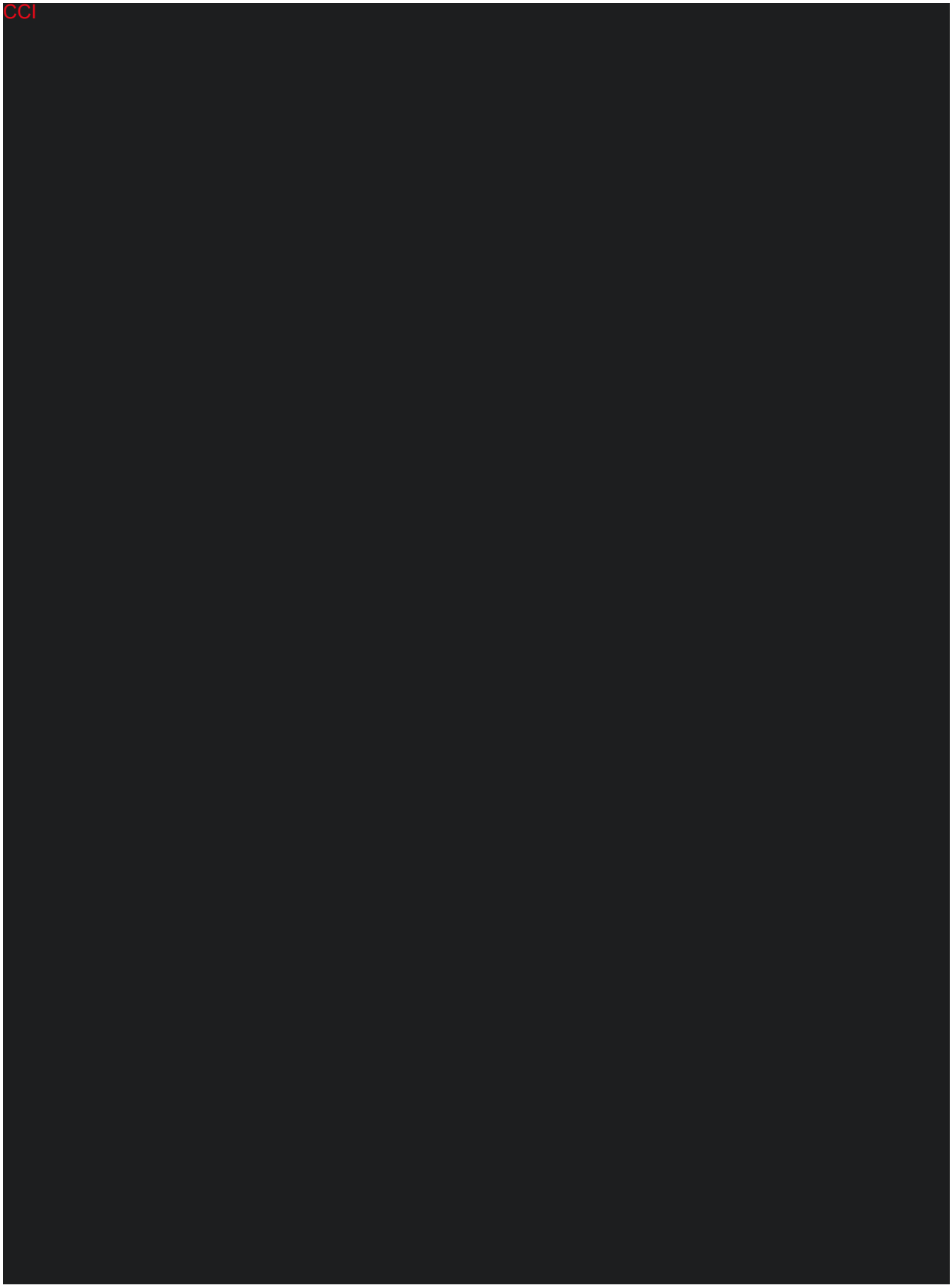
[redacted]

CCI



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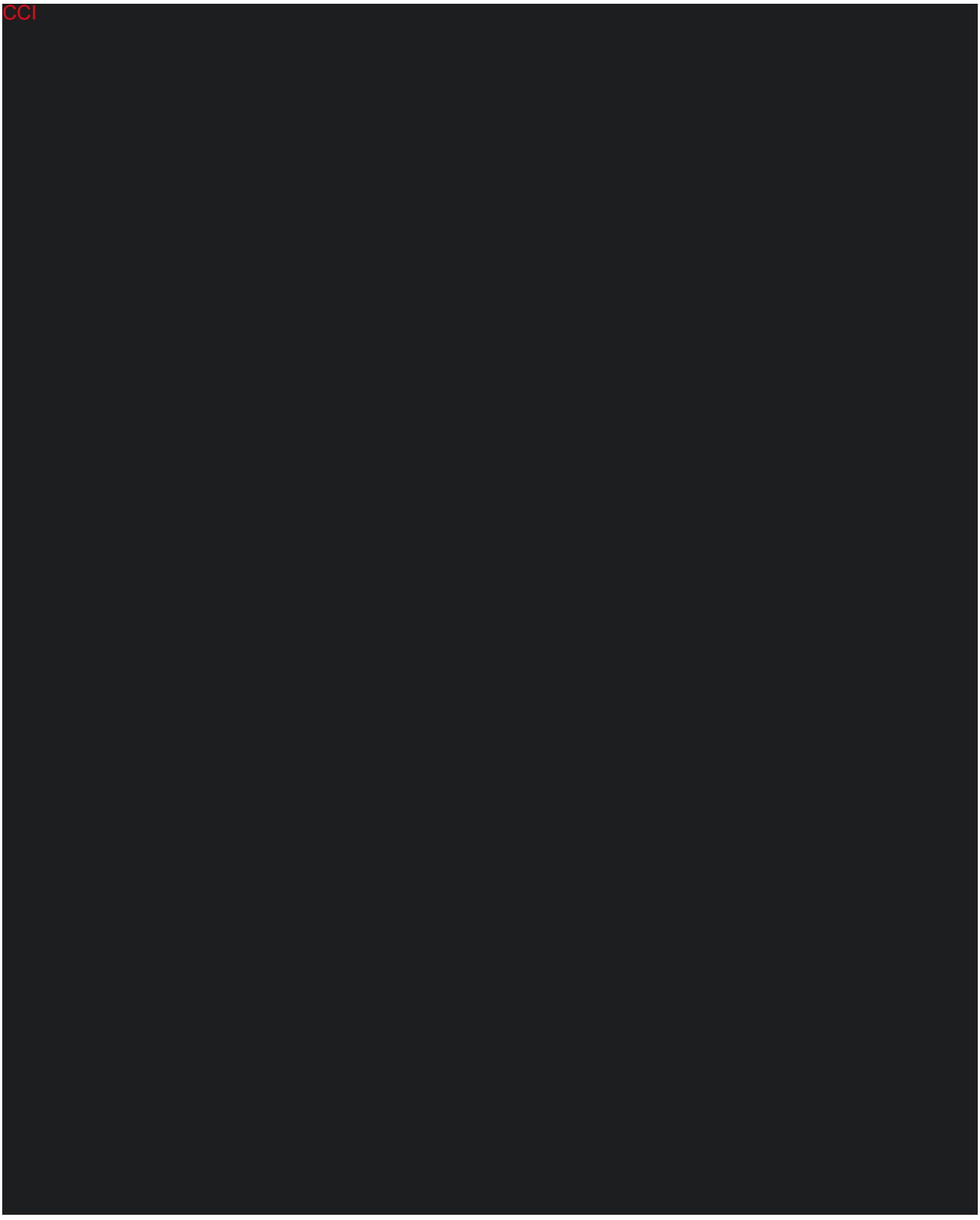

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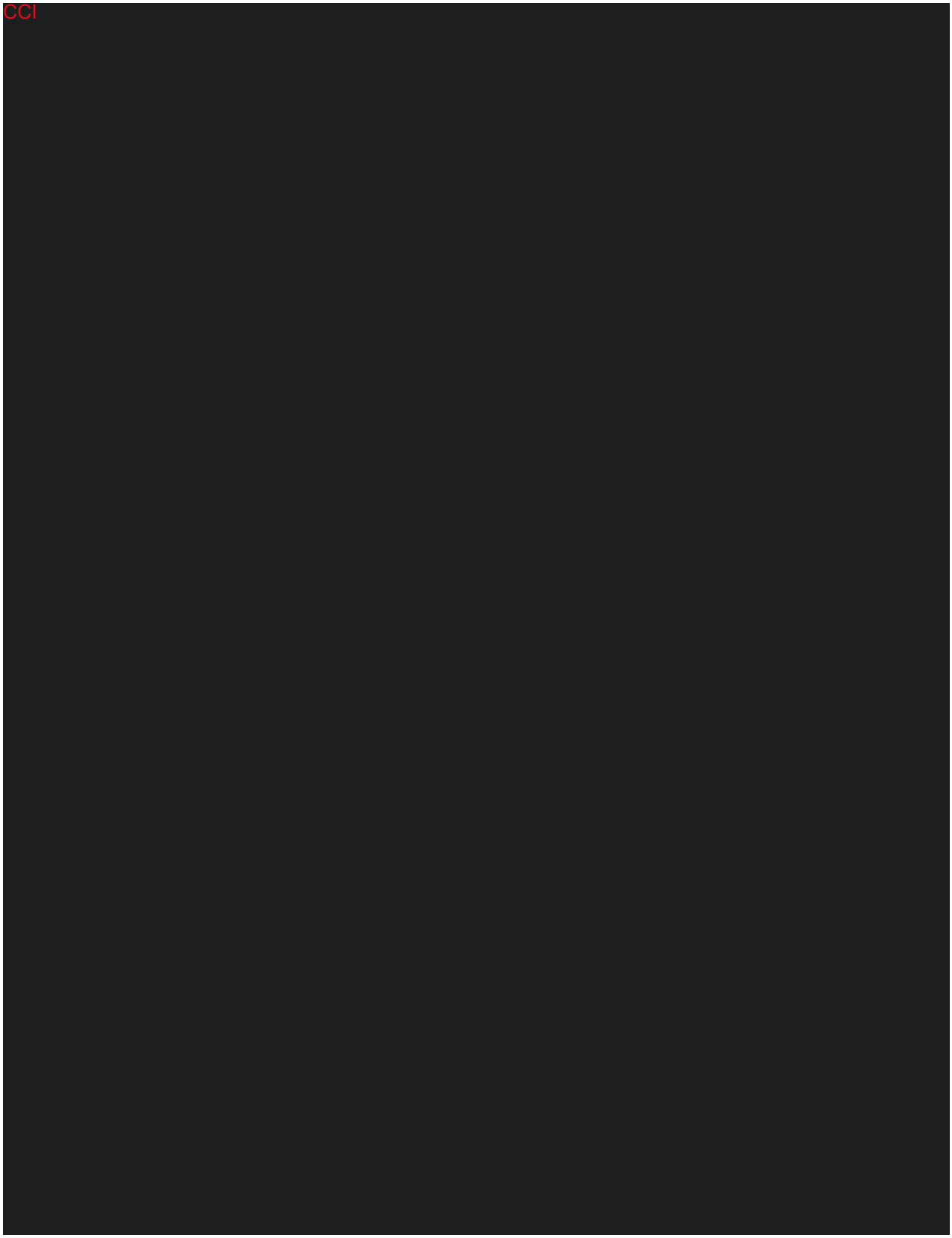

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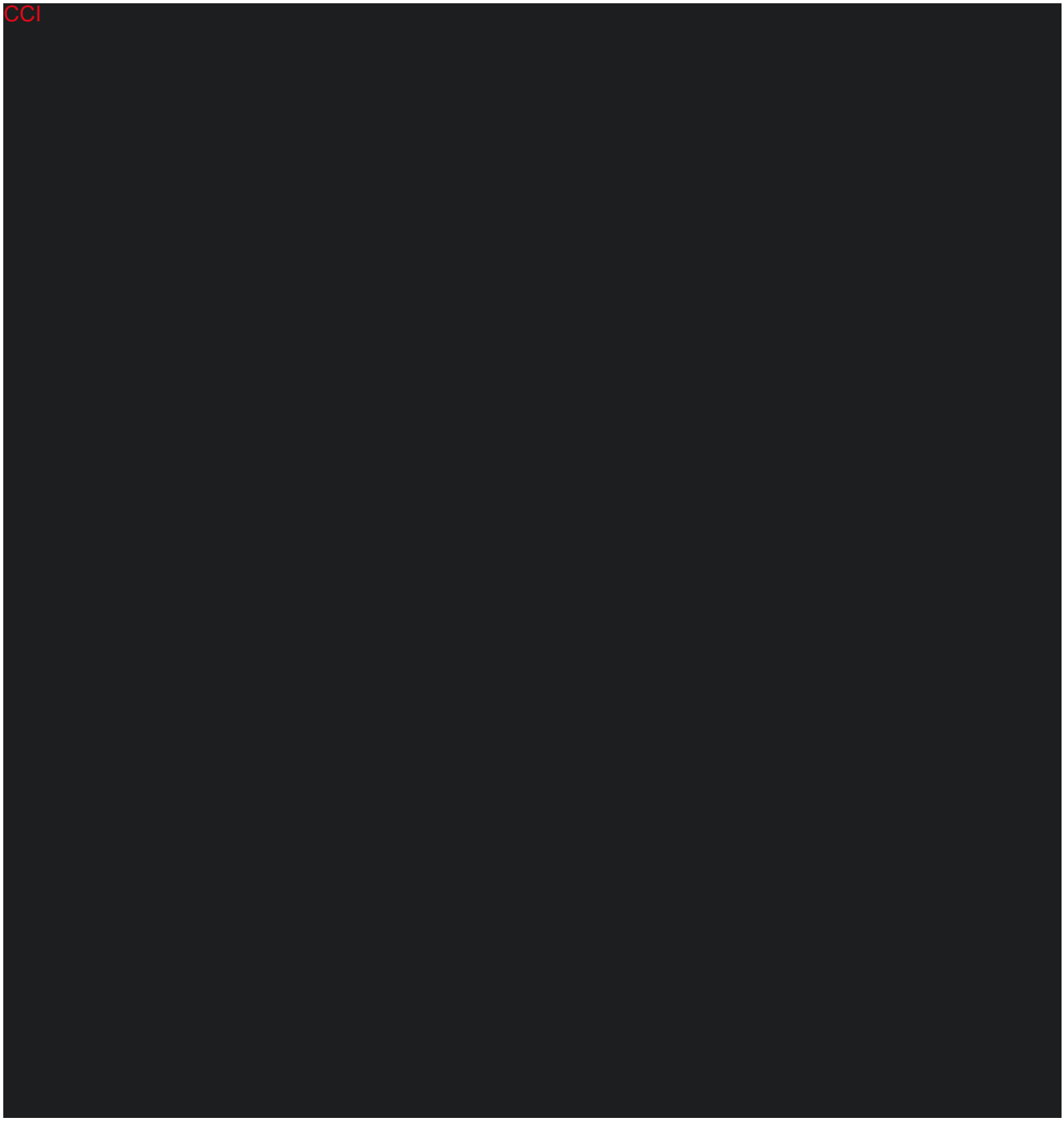

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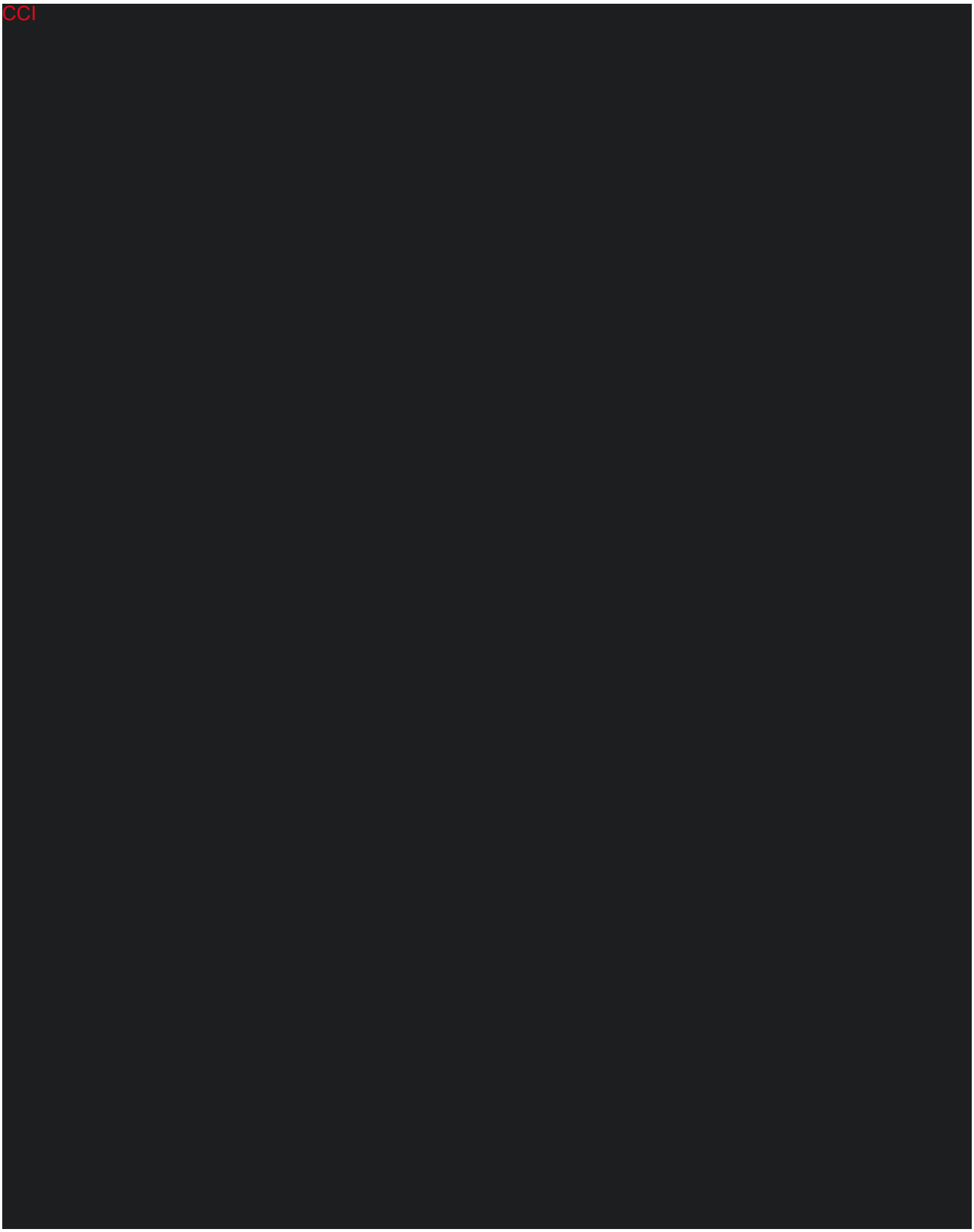

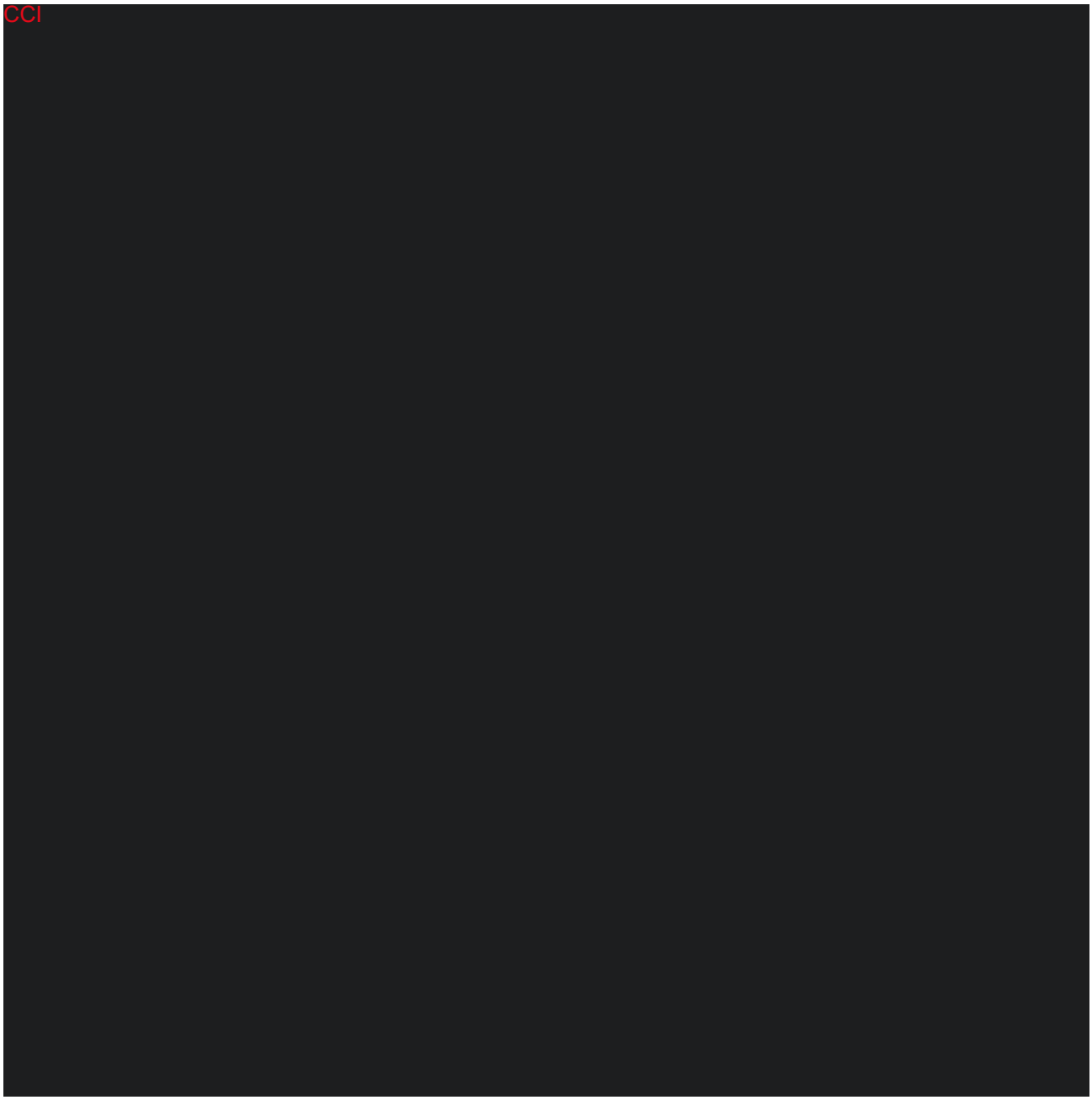
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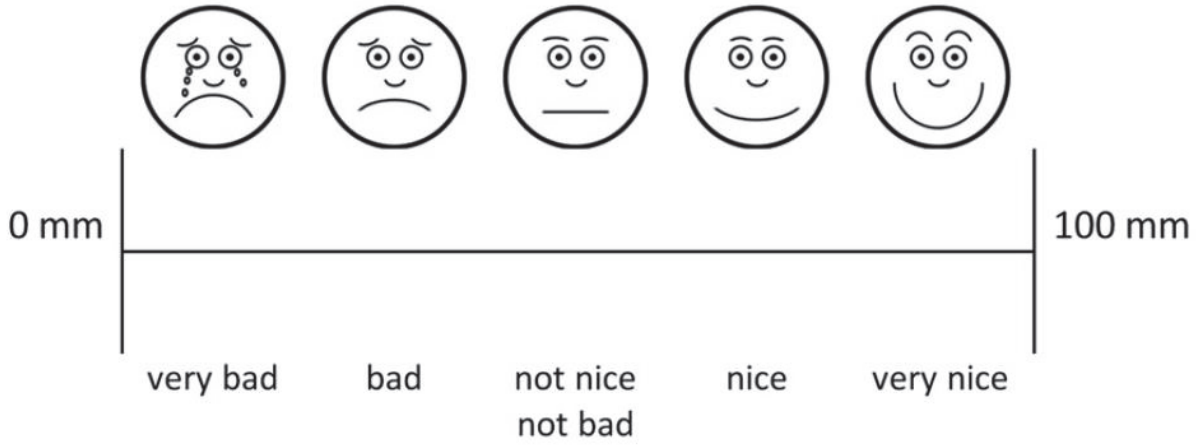
APPENDIX 9 THE TASTE AND PALATABILITY SURVEY

Please rate how your child reacted to the taste of the surufatinib oral suspension. Select one below.

- Very nice (Smiley-Face Scale 5)
- Nice (Smiley-Face Scale 4)
- Not nice, not bad (Smiley-Face Scale 3)
- Bad (Smiley-Face Scale 2)
- Very bad (Smiley-Face Scale 1)

Smiley-Face Scale



Source: Diane 2017.

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Signature Page for VV-CLIN-004023 v1.0

Approval Task	PPD 25-Jan-2023 23:51:42 GMT+0000

Signature Page for VV-CLIN-004023 v1.0

Signature Page for VV-CLIN-000935 v1.0

Approval	PPD 29-Jul-2022 07:47:36 GMT+0000

Signature Page for VV-CLIN-000935 v1.0