HUTCHMED

Clinical Study Protocol

A MULTICENTER, OPEN-LABEL PHASE I STUDY EVALUATING THE SAFETY AND TOLERABILITY OF HMPL-306 IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS WITH IDH MUTATIONS

Short Title	A Phase 1 Study of HMPL-306 in Locally Advanced Solid Tumors with IDH Mutations
Investigational Product(s):	HMPL-306
Protocol Number:	2020-306-GLOB2
Clinical Phase:	1
Date of Issue:	17 May 2022
Amendment:	2
Sponsor:	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
Regulatory Agency Identifier Number (s)	IND: 151196 EudraCT: 2020-003729-44

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonization (ICH) 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. Reconsent 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	A Multicenter, Open-Label Phase I Study Evaluating the Safety and Tolerability of HMPL-306 in Subjects with Locally Advanced or Metastatic Solid Tumors with IDH Mutations
Protocol Number	2020-306-GLOB2
Date of Issue	17 May 2022
Amendment	2

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: PPD , MD, MBA	**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 2020-306-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 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 subject's participation and all data required by the protocol

Name:	**Title:**	**Institution:**
Signature:		**Date:**

DOCUMENT HISTORY

Amendment	Version	Date of Issue
Original	1	18 Sep 2020
1	1	29 October 2020

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AMENDMENT SUMMARY

This 2020-306-GLOB2 Amendment 2 replaces the 2020-306-GLOB2 Amendment 1 protocol. 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 2 is to explore additional dose levels in Part 1. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Details of prior amendments are summarized in Appendix 12.

Section Number	Summary of Change	Rationale for Change
Title Page, Footers, Signature Page, and Globally	The Sponsor company name, address, and logo, where appropriate, were updated throughout.	The administrative updates were made to appropriately reflect the change of Sponsor company name.
Synopsis and Section 6 – Study Conduct	The approximate duration of the study was updated from 36 to 42 months to reflect the additional dose levels added to Dose Escalation.	The updates were made to be consistent with the additional dose levels added to Part 1.
Synopsis; Section 1.2 – Study Schematic; and Section 4.1.1 – Part 1 (Dose Escalation), Table 5 – Subject Dose Grouping (Dose Escalation Plan)	The Part 1 dose escalation language was updated to reflect the addition of dose levels 5, 6, 7, and 8, or CCI [redacted] mg dose levels, respectively.	The updates were made to further investigate PK exposure and PD effects at higher dose levels.
Synopsis and Section 3 – Objectives and Endpoints	The "Cohort C-1 Only" language was removed from the Part 2 exploratory objective.	The indicated language was removed as this exploratory objective applies to all cohorts.
Section 1.3 – Schedule of Events, Table 1 – Schedule of Events (excluding Cohort C-1) and Table 2 – Schedule of Events - Cohort C-1	The table was updated to include a pregnancy test on D1.	This test was added to align with global regulatory requests.
Section 1.3 – Schedule of Events, Table 1 – Schedule of Events (excluding Cohort C-1); and Section 6.1.14 – IDH Mutation Confirmation	The language was added to clarify that a fresh tissue biopsy is required if archival tissue is not available.	The language updates were made for clarity.
Section 1.3 – Schedule of Events; Table 1 – Schedule of Events (excluding Cohort C-1), Table 2 – Schedule of Events – Cohort C-1	The language was updated to clarify that the Ophthalmologic examination after the start of study drug administration must be ±1 week of D15 in cycle 2 in Table 1 and 2. In Table 2 language was added to clarify that Ophthalmologic examinations must be completed -1 week of D28 (day prior to surgery).	The language updates were made for clarification.
Section 1.3 – Schedule of Events, Table 2 – Schedule of Events – Cohort C-1	The language was updated to indicate that patients enrolled to the control arm will not need to	The language updates were made for clarity.

	undergo pharmacokinetic sampling during the pre-surgery period of the study. The language updates were made to clarify that tumor imaging must be submitted within 2 weeks after surgery for Cohort C-1, and only a brain scan is required at the surgery time point; other tumor imaging can be done if clinically indicated.	
Section 4.1.1 – Part 1 (Dose Escalation)	The language indicating that multiple subjects, with an additional maximum of 3 subjects, in screening when the last subject of the cohort starts treatment may be enrolled in this cohort with evaluation and consent from the Sponsor and investigator was removed. The language that discusses the rationale behind the addition of dose levels 5 to 8 was added.	The language was removed as the intent is only to enroll the predefined number of patient per cohort. The rationale language for dose levels 5 to 8 was added for clarity.
Section 4.1.2 – Part 2 (Dose Expansion)	The word "non-enhancing" was removed to indicate that Cohort C-1 will enroll 15 subjects with recurrent low grade glioma.	The language was removed as it is intended to allow Grade 3 gliomas to enroll who many have enhancing gliomas.
Section 4.2.2 – Rationale for Study Population Selection	The language referencing the updated Appendix 11 was added.	The language was added to provide an expanded discussion on the rationale for patient selection, and line of therapy for Cohorts A to D.
Section 4.2.3 – Rationale for Biomarker Testing	The language was updated to include CCI	The language updates were made for accuracy.
Section 5.2 – Inclusion Criteria	The language for criterion 14a was updated to include "non-enhancing". The language in criterion 8 was made to clarify that international normalized ratio of ≤1.5 or an activated partial thromboplastin time of ≤1.5 × ULN.	The language updates were made for accuracy and clarity.
Section 5.3 – Exclusion Criteria	The language in criterion 1 was updated to indicate that radiotherapy received <12 weeks for glioma subjects is an exclusion. Criterion 18 was added to exclude subjects with a known hypersensitivity to HMPL-306 or any of its excipients.	The language updates were made for clarity, accuracy, and safety reasons.
Section 6.1.10.10 – IDH Mutational Status	The language was updated to indicate that IDH mutations should be tested locally via a biopsy tissue collection at the clinical site.	The language update was made for clarity.

Section 6.1.13 – Tumor Assessment	The language updates were made to clarify when the tumor assessments will be performed during the study.	The language updates were made for clarity.
Section 6.2.1.1 – Permanent Discontinuation of Treatment	The language introducing the reasons for discontinuation was updated from "could" to "must be discontinued from treatment…" The language in Criterion 3 was updated to include adverse events that warrant withdrawal of study treatment as determined by principal investigator or as outlined in Section 7.4.2.	The language update was made to comply with regulatory requested change. The language update to Criterion 3 was for clarity and guidance.
Section 7.2.1 – Formulation, Storage, Preparation, and Handling	The language updates were remove "white" from the description of the high-density polyethylene bottles and add clarify that HMPL-306 should be stored with protection from light and moisture.	The language updates were made for clarity.
Section 9.1.2 – Sample Size Rationale and Section 9.1.2.1 – Dose Escalation Part	The number of estimated subjects to be recruited subjects was updated from 110 to 115 subjects to 122 to 131 subjects. The number of subjects in the dose escalation part was updated from 15 to 20 subjects to 27 to 36 subjects.	The number of subjects was updated to reflect the additional cohorts added to dose escalation.
Appendix 1 – PK, PD, and Biomarker Assessments (Excluding Cohort C-1)	The tables in Appendices 1 and 2 were updated to indicate an ECG is required at screening. The footnote 2 in Appendices 1 and 2 was updated to include CCI testing and to clarify testing schedule.	The language updates were made for clarity and accuracy.
Appendix 6 – CCI	Several CCI were deleted from Appendix 6 list, and 3 CCI were added.	List was revised based on clinical relevance.
Appendix 11 – Expanded Population Selection Rationale	Appendix was added to elaborate on the rationale for study patient, and line of therapy selection for Cohorts A to D.	The appendix was added to provide an expanded rationale for study patient selection, and line of therapy for Cohorts A to D.

LIST OF ABBREVIATIONS

Abbreviations	Definitions
2-HG	2-hydroxyglutaric acid
ADL	Activity of daily living
AE	Adverse event
α-KG	α-ketoglutaric acid
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
CI	Confidence interval
CL/F	Total plasma clearance of drug after extravascular administration
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration within the dosing interval (at steady state)
C_{trough}	Observed plasma concentration at the end of a dosing interval (taken directly before the next dose administration)
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	case report form
CRO	Contract research organization
CRR	Complete response rate
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria of Adverse Events
ctDNA	Circulating tumor DNA
CV%	Coefficient of variation
CxDx	Cycle x Day x
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviations	Definitions
EDC	Electronic data capture
EOT	End-of-treatment
FDG	^{18}F-fluorodeoxyglucose
FIH	First-in-human
FLAIR	Fluid-attenuated inversion recovery
GCP	Good Clinical Practice
Gd	Gadolinium
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e-antibody
HBeAg	Hepatitis B e-antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDH	Isocitrate dehydrogenase
IHC	Immunohistochemistry
IMP	Investigational medical product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
MedDRA	Medical Dictionary for Drug Regulatory Activities
mIDH	Mutant IDH
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval-2
MUGA	Multigated acquisition
NCI	National Cancer Institute
NGS	Next-generation sequencing
NOAEL	No observed adverse effect level
OATP1B3	Organic anion-transporting polypeptide 1B3

Abbreviations	**Definitions**
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PI	Principal Investigator
PO	Orally
PR	Partial response
PS	Performance status
pT	Toxicity probability
QD	Once a day
QT	Interval from the start of the Q wave to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SDV	Source data verification
SIV	Study Initiation Visit
SRC	Safety Review Committee
$t_{1/2}$	Elimination half-life
TLS	Tumor lysis syndrome
T_{max}	Time to peak plasma concentration
TEAE	Treatment-emergent adverse event
TTR	Time-to-response
UGT	Uridine diphosphate glucuronosyltransferase

1 PROTOCOL SUMMARY

1.1 Synopsis

Title	A Multicenter, Open-Label Phase I Study Evaluating the Safety and Tolerability of HMPL-306 in Subjects with Locally Advanced or Metastatic Solid Tumors with IDH Mutations
Short Title	A Phase 1 Study of HMPL-306 in Locally Advanced Solid Tumors with IDH mutations
Acronym	Not applicable
Phase	1
Rationale	Isocitrate dehydrogenase (IDH) is a rate-limiting enzyme in the tricarboxylic acid cycle participating in cellular energy metabolism and catalyzes the oxidative decarboxylation of isocitrate to generation of α-ketonyl acetylbenzoic acid glutarate (α-KG) and carbon dioxide. There are 3 isoforms of IDH enzymes in the human body, namely IDH1 located in cell cytoplasm, IDH2 in the mitochondria, and IDH3 in the mitochondria. IDH1 or IDH2 mutations or co-mutations have been associated with various tumors, including glioma, chondrosarcoma, and cholangiocarcinoma. HMPL-306 is a novel, small-molecule, orally available, highly selective, and potent inhibitor of mutant IDH. It demonstrated a remarkable inhibitory effect on 2-hydroxyglutaric acid (2-HG) in tumor cells with IDH mutations, and therefore, this phase 1 open-label study is planned to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations.
Target Population	Adult male and female subjects ≥18 years of age with locally advanced or metastatic solid tumors with any IDH mutation. Part 1: locally advanced or metastatic solid tumors Part 2: • Cohort A: Cholangiocarcinoma • Cohort B: Skeletal chondrosarcoma • Cohort C: Low-grade glioma ○ Cohort C-1: Perioperative glioma • Cohort D: Any other solid tumor harboring an IDH mutation
Intervention	Part 1 (dose escalation): CCI [redacted] mg HMPL-306 orally (PO) once daily (QD) Part 2 (dose expansion): recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) from Part 1 PO QD

Objectives and Endpoints	
Objectives	**Corresponding Endpoints**
Primary: **Part 1 – Dose Escalation:** To evaluate the safety and tolerability of HMPL-306, thereby determining the RP2D and/or the MTD of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	**Primary:** Safety including dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), electrocardiograms (ECGs), and clinical laboratory abnormalities MTD and/or RP2D
Part 2 – Dose Expansion: To characterize the safety and tolerability of HMPL-306 in subjects with locally advanced or metastatic solid tumors with an IDH mutation	Safety including TEAEs, SAEs, ECGs, and clinical laboratory abnormalities
Part 2 – Cohort C-1 Only: To determine the 2-HG concentration in surgically resected tumors following pre-surgical treatment with HMPL-306 when compared to untreated tumors	Observed plasma and tumor concentrations of 2-HG
Secondary: **Part 1 and Part 2:** To assess the preliminary antitumor activity of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	**Secondary:** Objective response rate, disease control rate, duration of response, time to response, and progression-free survival
Part 1 and Part 2: To assess the pharmacokinetics (PK) of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	Observed plasma concentrations and PK parameters of HMPL-306
Part 1 and Part 2: To assess the pharmacodynamics (PD) of HMPL-306 in subjects with locally advanced or metastatic solid tumors with an IDH mutations	Observed plasma concentrations of 2-HG
Part 2 – Cohort C-1 Only: To characterize the safety and tolerability of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	Safety including, TEAEs, SAEs, deaths, ECGs, and clinical laboratory abnormalities
Exploratory: **Part 1 and Part 2:** To explore the relationship between HMPL-306 PK exposure and 2-HG levels and percent inhibition	**Exploratory** Changes from baseline in tumor markers, correlation with drug exposure, and association with efficacy and safety parameters
Part 1 and Part 2: To explore the influence of gene abnormalities other than IDH mutations on safety, efficacy, PD, and PK	
Part 1 and Part 2: To assess the potential predictive biomarkers or response or progression though collection of serial circulating tumor DNA collection	
Part 2: To explore the relationship between the changes in the frequency of genetic mutation, efficacy, PK, PD, and safety after HMPL-306 treatment in tumor and plasma	
Part 2 – To assess the overall survival (OS) in subjects enrolled to expansion Cohorts A, B, and D.	OS

Brief Summary: This is a phase 1, open-label, multicenter study to evaluate the safety and tolerability of HMPL-306 administered orally in the treatment of subjects with locally advanced or metastatic solid tumors with IDH mutation. The study consists of 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). The dose escalation part will determine the MTD/RP2D. The dose expansion part will administer the MTD/RP2D to 4 cohorts of subjects:

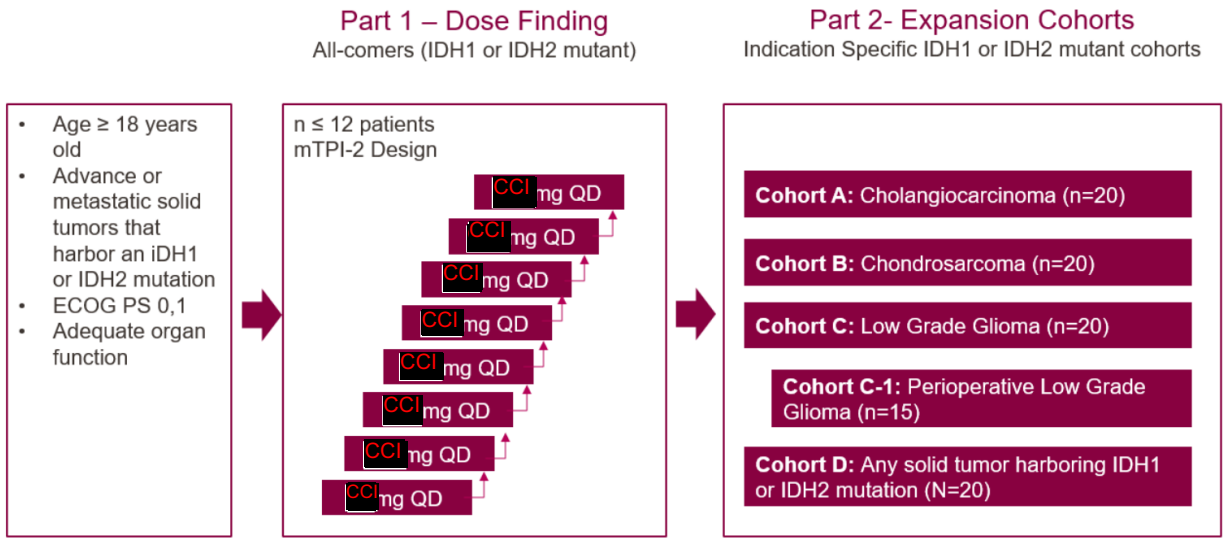
- **Cohort A**: Cholangiocarcinoma
- **Cohort B**: Skeletal chondrosarcoma
- **Cohort C**: Low-grade glioma
  - **Cohort C-1**: Perioperative glioma
- **Cohort D**: Any other solid tumor harboring an IDH mutation

Condition/Disease	Locally advanced solid tumors with IDH mutation
Study Duration	Approximately 42 months
Treatment Duration	28-day continuous dosing treatment cycle
Health Measurement/Observation	This study will determine the MTD and/or RP2D, as well as safety assessments including DLTs, TEAEs, SAEs, deaths, ECGs, and clinical laboratory abnormalities. During the dose expansion part, subjects will receive HMPL-306 at MTD or RP2D for 28 days in each cycle until disease progression, death, intolerable toxicity, the subject can no longer benefit from the study treatment at the investigator's discretion, withdrawal of consent, lost to follow-up, death, or the end of study, whichever comes first. For Cohort C-1, all subjects will have the option of receiving HMPL-306 following surgery. Subjects with no residual disease following surgery will be allowed to receive HMPL-306 for up to 1 year or until disease progression, whichever occurs first. If residual disease is evident following surgery, those subjects may receive HMPL-306 until disease progression.
Visit Frequency	Cycle 1: every week (±1 day, except D1) Cycle 2: every 2 weeks (±1 day) Cycle 3 and onward: Day 1 (±3 days) End of Treatment: within 7 days (±3 days) after the last dose **For Cohort C-1:** Pre-surgery: every week (±1 day, except D1) Cycles 1 and 2: every 2 weeks (±3 days) Cycle 3 and onward: Day 1 (±3 days) End of Treatment: within 7 days (±3 days) after the last dose
Number of Participants	Part 1: at least 1 subject will be enrolled to dose levels 1, 2, and 3. At least 3 subjects will be enrolled to dose levels 4, 5, 6, 7, and 8. Part 2: approximately 20 evaluable subjects (15 subjects in Cohort C-1) per cohort will be enrolled; for a total of approximately 95 subjects
Intervention Groups and Duration	Part 1: CCI [redacted], and CCI mg of HMPL-306 PO QD administered to dosing groups for 28 days cycles Part 2: MTD/RP2D as determined in Part 1, administered PO QD to approximately 95 subjects for 28-day cycles
Data Monitoring/Other Committee	Yes

1.2 Study Schematic

The study schematic is presented in Figure 1.

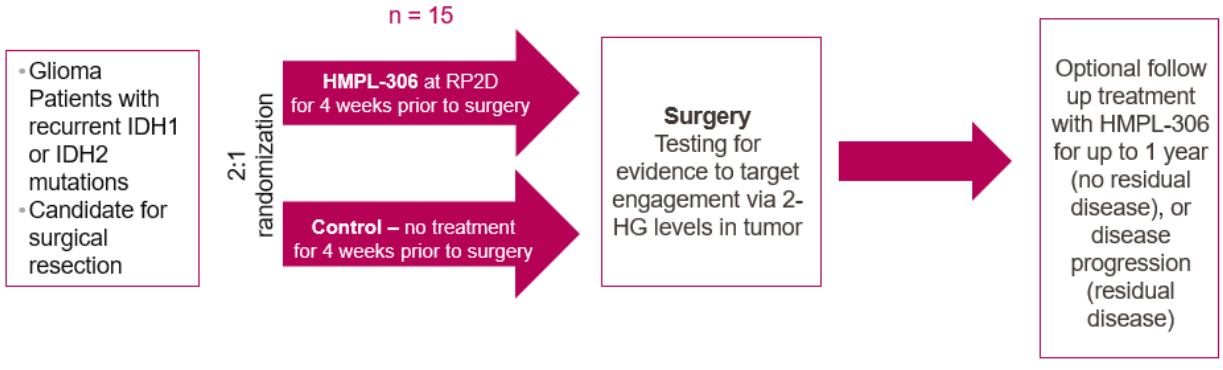
Figure 1 Study Schema



ECOG = Eastern Cooperative Oncology Group; IDH = isocitrate dehydrogenase; mTPI-2 = modified toxicity probability interval-2; PS = performance status; QD = once daily.
Note: Subjects in dose expansion must have documented mutations.

The study schematic for Cohort C-1 is presented in Figure 2.

Figure 2 Study Schema, Cohort C-1



2-HG = 2-hydroxyglutaric acid; IDH = isocitrate dehydrogenase; MRI = magnetic resonance imaging; PK = pharmacokinetics.

1.3 Schedule of Events

The schedule of events (SOE) is presented in Table 1 and Table 2.

Table 1 Schedule of Events (excluding Cohort C-1)

Cycle/Period	**Pre-screening**	**Screening**	**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit			**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 Days After the Last Dose**	**30 Days After the EOT Visit**	**Every 12 Weeks From EOT Visit**	**Every 12 Weeks From EOT Visit**
Visit Window (days)	**--**	**-28 to -1**	**--**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities													
Pre-screening informed consent[1]	X												
Main informed consent[2]		X											
IDH mutational status[3]	X	X								X			
Medical history and demographics[4]	X	X											
Prior and concomitant medications and concomitant procedures[5]		X	X	X	X	X	X	X	X	X	X	X	
Height		X											
Physical examination, vital signs, and weight[6]		X	X	X	X	X	X	X	X	X			
ECOG performance status[6]		X	X		X		X	X	X	X			
Ophthalmologic examination[7]		X						X (±1 week)	Every 12 weeks (±1 week) from C4D1				
Laboratory evaluations[6]													
Hematology[8]		X[9]		X	X	X	X	X	X	X	X		
Blood chemistry[10]		X[9]		X	X	X	X	X	X	X	X		
Blood amylase and lipase		X[9]		X	X	X	X	X	X	X			
Fasting lipid panel[11]		X[9]			X		X		X	X			
Coagulation indicators[12]		X[9]			X		X		X				
Pregnancy test[13]		X	X				X		X	X	X		
Urinalysis[14]		X[9]					X		X	X			

Table 1 Schedule of Events (excluding Cohort C-1)

Cycle/Period	**Pre-screening**	**Screening**	**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit			**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 Days After the Last Dose**	**30 Days After the EOT Visit**	**Every 12 Weeks From EOT Visit**	**Every 12 Weeks From EOT Visit**
Visit Window (days)	**--**	**-28 to -1**	**--**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities													
Virological screening[15]		X											
HbA1C		X[9]			X		X		X	X			
PK and PD assessments	Refer to Appendix 1												
12-lead ECG[6,16]	Refer to Appendix 1												
ECHO/MUGA scan		X					X		C3D1 then Day 1 of every odd cycle (ie, C5D1, C7D1, etc.) (±1 week)				
Tumor evaluation/imaging[17]		X	Every 8 weeks from C1D1 during the first 24 (±1) weeks and every 12 (±2) weeks thereafter									X	
Tumor tissue for exploratory biomarker evaluation. Applies to Cohorts A, B, and D only[18]		X					X±7 days		At disease progression only in dose expansion				
Blood for gene mutation analysis[19]		X	Only in dose expansion; refer to Appendix 1										
Study drug administration		Dosing will be based on cohort for dose escalation, and will be dosed at the RP2D in dose expansion											
AEs[20]	X	X	X	X	X	X	X	X	X	X	X		
Survival follow-up[21]													X

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; C = cycle; CMV = cytomegalovirus; ctDNA = circulating tumor DNA; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; FFPE = formalin-fixed paraffin-embedded; HbA1C = glycated hemoglobin; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e-antibody; HBeAg = hepatitis B e-antigen; HBsAb = hepatitis B surface antibody; HBsAb = hepatitis B s-antigen;

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IDH = isocitrate dehydrogenase; INR = international normalized ratio; LDH = lactate dehydrogenase; MUGA = multigated acquisition; NGS = next-generation sequencing; PCR = polymerase chain reaction; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PT = prothrombin time; RNA = ribonucleic acid; RP2D = recommended phase 2 dose; SAE = serious adverse event

1. Pre-screening informed consent must be obtained for subjects who do not have IDH mutational status report. The pre-screening consent should be signed before any study-related examinations or procedures are performed. Subjects who have already tested positive for IDH mutation may enter Screening period directly.
2. Written informed consent must be obtained before any study-related examinations or procedures are performed. However, before informed consent is obtained, if the assessments for standard treatment are performed within 28 days before the planned Day 1 of Cycle 1, they can be used to replace the assessments during the Screening Period without repeating the examinations except for assessments that need to be performed 7 days before the start of the study drug administration. If there is dosing on the assessment day, all assessments should be completed before the study drug administration, except 12-lead ECG, ECHO/MUGA scan, ophthalmologic assessments, and efficacy assessments.
3. Subjects should have a local report of IDH mutational analysis, confirming mutant IDH. Further, during Screening, tumor tissue samples will be collected and provided to a central laboratory for IDH mutations confirmation. If archival tissue is not available, a biopsy will be required to collect fresh tissue for central testing. Tissue collection for IDH testing at EOT is for patients in dose expansion only.
4. Medical history data include significant clinical disease or symptom, surgical history, history of malignancy (including date of diagnosis; classification and prognosis evaluation of the study disease, the treatment performed, and the outcome; and the tumor type and outcomes of any other previous malignancies), smoking history, history of alcohol consumption, history of drug abuse, and other medical-related history. Demographic information includes sex, race, and in some countries, year of birth.
5. Concomitant medications include any prescription and over-the-counter medications. During the Screening Period, all drugs used by the subject within 28 days prior to the start of study drug administration should be recorded in the eCRF. In subsequent visits, the drugs used by that period and within 30 days after termination of treatment should be recorded in the eCRF. Subsequent new antitumor treatment regimens, during the Safety, and Efficacy Follow-up Periods will also be recorded.
6. Physical examination, vital signs, weight, ECOG performance status score, laboratory evaluations, and ECG (unless otherwise stipulated) should be obtained within the scheduled visit date. During Cycle 1 and Cycle 2, all visits should be completed ±1 day of the scheduled date unless otherwise stipulated. Starting from Cycle 3, unless otherwise stipulated, visits during treatment should be completed within ±3 days of the scheduled date. Unscheduled examinations may be performed if clinically indicated.
7. Ophthalmologic assessments, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, optical coherence tomography (OCT), and intraocular pressure will be performed during the Screening Period. If the subject has undergone the relevant examinations 60 days before the start of study treatment (C1D1), they need not be repeated. After the start of study drug administration, OCT will be performed at 6 weeks (±1 week), then OCT, eye appearance, and slit lamp examinations will be performed every 12 weeks (±1 week) from C4D1 and at the EOT visit. Other ophthalmic examinations are to be performed when clinically indicated. If the subject develops an ophthalmic AE related to HMPL-306, the frequency of the examination should be increased to once every cycle until the adverse event is relieved or stable.
8. Hematology includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential and classifications (absolute neutrophil count, neutrophils % absolute lymphocyte count, lymphocytes %, absolute eosinophil count, eosinophils %, absolute monocyte count, monocytes %, absolute basophil count and basophils %), and platelet count. If abnormal or primitive immature cells are seen, they are also required to be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.
9. These tests should be completed within 7 days before the start of treatment; if completed more than 7 days before the first dose, they must be repeated on C1D1 prior to dosing.
10. Blood chemistry includes blood urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, creatine phosphokinase, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, LDH, total protein, and albumin.
11. Fasting lipid panel includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.
12. Coagulation indicators include PT, aPTT, and INR.
13. Female subjects of childbearing potential (including those who have undergone tubal ligation) must undergo a serum pregnancy test within 7 days before drug administration and record a negative result. After enrollment, serum or urine pregnancy test should be conducted on Day 1 of every treatment cycle starting from Cycle 1, at EOT visit, and during Safety Follow-up Period. Unscheduled testing can be performed if there is an indication.
14. Urinalysis includes glucose, protein, ketone body, red blood cells, white blood cells, and urobilinogen.
15. Only required if subject has finding suggestive of active viral infection. Virological screening includes HIV, HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), HCV (HCV antibody), and CMV (CMV antibody). If HBsAg or HBcAb or CMV antibody is positive, CMV DNA or HBV DNA is also required to be assayed by PCR method.

If CMV DNA or HBV DNA is negative, subjects may be enrolled and their CMV DNA or HBV DNA should be monitored every cycle). If HCV antibody is positive, HCV RNA is required to undergo PCR testing.

16. ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate. Evaluation time points are shown in Appendix 1. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated.
17. De-identified tumor imaging with study number is to be transmitted to central vendor for image storage.
18. In the expansion part, for subjects participating in the exploratory portion of the study, at the disease progression or EOT, tumor tissues (FFPE block or section, or fresh tissue from a biopsy) will be collected to check IDH mutation status and other co-occurring genes alterations to explore the resistance mechanism of HMPL-306.
19. ctDNA samples will be collected in the escalation and expansion part.
20. AEs due to the protocol-required intervention (ex. NGS testing) will be collected in the pre-screening phase. AEs will be collected from signing of the main informed consent until 30 days after the last dose or initiation of new antitumor therapy. The relevant AEs will be followed up until they are recovered to the baseline status, already in a stable state as assessed by the investigator, start of new antitumor therapy, loss to follow-up, death, withdrawal of informed consent, or it has been confirmed the AEs are unrelated to the study drug. SAEs are collected from the signing of the informed consent form until 30 days after the last dose or initiation of new antitumor therapy and until resolution regardless of relationship to study treatment.
21. All subjects in dose expansion cohort A, B, and D may be followed for survival status every 12 weeks (±14 days) up to 2 years from EOT visit, until death, lost to follow up, or withdrawal of consent. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

Table 2 Schedule of Events – Cohort C-1

Cycle/Period	**Pre-screening**	**Screening**	**Pre-Surgery**					**Surgery**	**C1+[1]**		**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**
Visit			**D1**	**D8**	**D15**	**D22**	**D28 (Day prior to surgery)**		**D1**	**D15**	**D1**	**D15**	**D1**	**Within 7 Days After the Last Dose**	**30 Days After the EOT Visit**	**Every 12 Weeks From EOT Visit**
Visit Window (days)	**--**	**-28 to -1**	**--**	**±1**	**±1**	**±1**	**--**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±14**
Activities																
Pre-screening informed consent[2]	X															
Main Informed consent[3]		X														
IDH mutational status[4]	X	X												X		
Medical history and demographics[5]	X	X														
Prior and concomitant medications and concomitant procedures[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X														
Physical examination, vital signs, and weight[7]		X			X		X		X	X	X	X	X	X		
ECOG performance status[7]		X			X		X		X		X		X	X		
Ophthalmologic examination[8]		X					X[9] (-1 week)					X[9] (±1 week)	Every 12 weeks (±1 week) from C4D1			
Laboratory evaluations:																
Hematology[10]		X[11]		X	X	X	X		X	X	X	X	X	X	X	
Blood chemistry[12]		X[11]		X	X	X	X		X	X	X	X	X	X	X	
Blood amylase and lipase		X[11]		X	X	X	X		X	X	X	X	X	X		
Fasting lipid panel[13]		X[11]			X		X		X		X		X	X		
Coagulation indicators[14]		X[11]			X		X		X		X		X			

Table 2 Schedule of Events – Cohort C-1

Cycle/Period	**Pre-screening**	**Screening**	**Pre-Surgery**					**Surgery**	**C1+[1]**		**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**
Visit			**D1**	**D8**	**D15**	**D22**	**D28 (Day prior to surgery)**		**D1**	**D15**	**D1**	**D15**	**D1**	**Within 7 Days After the Last Dose**	**30 Days After the EOT Visit**	**Every 12 Weeks From EOT Visit**
Visit Window (days)	**--**	**-28 to -1**	**--**	**±1**	**±1**	**±1**	**--**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±14**
Activities																
Pregnancy test[15]		X	X				X		X		X		X	X	X	
Urinalysis[15,16]		X[11]					X		X		X		X			
Virological screening[17]		X														
HbA1C		X[11]			X		X		X		X		X			
PK and PD assessments[18]			Refer to Appendix 2													
12-lead ECG[7, 19]		X	Refer to Appendix 2													
ECHO/MUGA scan		X							X		X		C3D1 then Day 1 of every odd cycle (ie, C5D1, C7D1, etc.) (± 1 week)			
Tumor evaluation/imaging[20]		X						X within 2 weeks post op	Every 8 weeks from C1D1 during the first 24 (±1 week) weeks and every 12 (±2 weeks) weeks thereafter							X
Blood for gene mutation analysis		X							Refer to Appendix 2							
Study drug administration			HMPL-306 will be dosed at the RP2D						HMPL-306 will be dosed at the RP2D							
AEs[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; C = cycle; CMV = cytomegalovirus; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOT = end of treatment; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e-antibody; HBeAg = hepatitis B e-antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B s-antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IDH = isocitrate dehydrogenase; INR = international normalized ratio; LDH = lactate dehydrogenase; MUGA = multigated acquisition; NGS = next-generation sequencing; PCR = polymerase chain reaction; PD = pharmacodynamic(s); PI = principal investigator; PK = pharmacokinetic(s); PT = prothrombin time; RNA = ribonucleic acid; RP2D = recommended phase 2 dose; SAE = serious adverse event.

1. If the subject chooses to continue treatment with HMPL-306, C1 will begin 4 to 8 weeks after surgery based on the clinical judgment of the PI.
2. Pre-screening informed consent is signed to obtain IDH mutational status report. Subjects who have already tested positive for IDH mutation may enter the Screening period directly.
3. Written informed consent must be obtained before any study-related assessments or procedures are performed. However, before informed consent is obtained, if the examinations for standard treatment are performed within 28 days before the planned Day 1 of Cycle 1, they can be used to replace the examinations during the Screening Period without repeating the examinations, except for examinations that need to be performed 7 days before the start of the study drug administration, as specified in the table. For subjects enrolled in dose escalation, all screening examinations should be completed before study drug administration on Day -7. If there is dosing on the assessment day, all assessment examinations should be completed before the study drug administration, except 12-lead ECG, ECHO/MUGA scan, ophthalmologic examination, and efficacy assessments.
4. Subjects who have reports of positive IDH1 and/or IDH2 mutation tests may directly enter the Screening Period.
5. Medical history data include significant clinical disease or symptom, surgical history, history of malignancy (including date of diagnosis; classification and prognosis evaluation of the study disease, the treatment performed, and the outcome; and the tumor types and outcomes of any other previous malignancies), smoking history, history of alcohol consumption, history of drug abuse, and other medical-related history. Demographic information includes sex, race, and in some countries, date of birth.
6. Concomitant medications include any prescription and over-the-counter medications. During the Screening Period, all drugs used for the subject within 28 days prior to the start of study drug administration should be recorded in the eCRF. In subsequent visits, the drugs used by that period and within 30 days after termination of treatment should be recorded in the eCRF. Subsequent new antitumor treatment regimens during the Safety and Efficacy Follow-up Periods will also be recorded.
7. Physical examination, vital signs, weight, ECOG performance status score, weight measurement, laboratory evaluations, and ECG (unless otherwise stipulated) should be obtained within the scheduled visit date. During Cycle 1 and Cycle 2, all visits should be completed ±1 day of the scheduled date unless otherwise stipulated. Starting from Cycle 3, unless otherwise stipulated, visits during treatment should be completed ±3 days of the scheduled date. Unscheduled examinations may be performed if clinically indicated.
8. Ophthalmologic assessments, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, optical coherence tomography (OCT), and intraocular pressure will be performed during the Screening Period. If the subject has undergone the relevant examinations 60 days before the start of study treatment (C1D1), they need not be repeated. After the start of study drug administration, OCT will be performed at 6 weeks (±1 week), then OCT, eye appearance, and slit lamp examinations will be performed every 12 weeks (±1 week) from C4D1 and at the EOT visit. Other ophthalmic examinations are to be performed when clinically indicated. If the subject develops an ophthalmic AE related to HMPL 306, the frequency of the examination should be increased to once every cycle until the AE is relieved or stable
9. Only for patients receiving HMPL-306.
10. Hematology includes red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils absolute neutrophil count and neutrophils %], lymphocytes [absolute lymphocyte count and lymphocytes %], eosinophils [absolute eosinophil count and eosinophils %], monocytes [absolute monocyte count and monocytes %], and basophils [absolute basophil count and basophils %), and platelet count. If abnormal or primitive immature cells are seen, they are also required to be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.
11. These tests should be completed within 7 days before the start of treatment; if completed more than 7 days before the first dose, they must be repeated on C1D1 prior to dosing.
12. Blood chemistry includes blood urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, creatine phosphokinase, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, LDH, total protein, and albumin.
13. Fasting lipid panel includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.
14. Coagulation indicators include PT, aPTT, and INR.

15. Female subjects of childbearing potential (including those who have undergone tubal ligation) must undergo a serum pregnancy test within 7 days before drug administration and record a negative result. After enrollment, serum or urine pregnancy test should be conducted on, Day 1 of every treatment cycle starting from Cycle 1, at EOT visit, and during Safety Follow-up Period. Unscheduled testing can be performed if there is an indication.
16. Urinalysis includes urine glucose, protein, ketone body, red blood cells, white blood cells, and urobilinogen.
17. Only required if subject has finding suggestive of active viral infection. Virological screening includes HIV, HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), HCV (HCV antibody), and CMV (CMV antibody). If HBsAg or HBcAb or CMV antibody is positive, CMV DNA or HBV DNA is also required to be assayed by PCR method. If CMV DNA or HBV DNA is negative, subjects may be enrolled and their CMV DNA or HBV DNA should be monitored every cycle. If HCV antibody is positive, HCV RNA is required to undergo PCR testing.
18. Patient enrolled to the control arm will not need to undergo PK sampling during the pre-surgery period of the study.
19. The 12-lead ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate. Evaluation time points are shown in Appendix 2. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated.
20. De-identified tumor imaging with study number is to be transmitted to central vendor for image storage. Only the brain scan is required at the surgery time point, but other tumor imaging may be done if clinically indicated. Tumor imaging must be transmitted to the central vendor for image storage within 2 weeks after surgery.
21. AEs due to the protocol-required intervention (NGS testing) will be collected in the pre-screening phase. AEs will be collected from signing of the informed consent until 30 days after the last dose or initiation of new antitumor therapy. The relevant AEs will be followed up until they are recovered to the baseline status, already in a stable state as assessed by the investigator, start of new antitumor therapy, loss to follow-up, death, withdrawal of informed consent, the end of study, or it has been confirmed the AEs are unrelated to the study drug. SAEs are collected from the signing of the informed consent form until 30 days after the last dose or initiation of new antitumor therapy, whichever is earlier and until resolution regardless of relationship to study treatment.

2 INTRODUCTION

2.1 Study Rationale

2.1.1 Investigational Product

HMPL-306 is an innovative, small-molecule, orally available, highly selective, and very potent inhibitor of both isocitrate dehydrogenase (IDH) 1 mutants and IDH2 mutants.

2.1.2 Isocitrate Dehydrogenase

Isocitrate dehydrogenase is a rate-limiting enzyme in the tricarboxylic acid cycle participating in cellular energy metabolism and catalyzes the oxidative decarboxylation of isocitrate to generation of α-ketonyl acetylbenzoic acidglutarate (α-KG) and carbon dioxide. There are 3 isoforms of IDH enzymes in the human body, namely IDH1 located in cell cytoplasm, IDH2 in mitochondria, and IDH3 in mitochondria (Wang 2013, Yoshihara 2001).

2.1.2.1 Mutations of IDH

IDH1 or IDH2 mutations or co-mutations have been associated with various tumors, including glioma, chondrosarcoma, and cholangiocarcinoma (Kosmider 2010, Marcucci 2010, Pardanani 2010, Yan 2009). Mutations or co-mutations involving IDH1 and or IDH2 in tumor cells lead to abnormal functions, whereby mutant IDH converts α-KG into carcinogenic metabolite (R)-2-hydroxyglutarate (2-HG) (Dang 2009, Fathi 2012). Accumulation of 2-HG in cells leads to series of epigenetic changes, including hypermethylation of deoxyribonucleic acid (DNA) and histone proteins, causing blockade of cell differentiation (Chowdhury 2011, Koivunen 2012, Xu 2011).

2.1.2.2 Mutations and Malignancies

Glioma is the most common intracranial malignant tumor, accounting for about 40% to 50% of all intracranial tumors. Studies have found that the incidence of IDH1 mutation in secondary glioma is more than 75% (Parsons 2008). At present, the IDH1 mutation inhibitors ivosidenib, BAY-1436032, and DS-1001 and the IDH1/IDH2 mutation inhibitor vorasidenib (AG-881) are being clinically evaluated for their therapeutic effect on gliomas with IDH1 mutation. In phase 1 clinical studies, the disease control rate of ivosidenib and vorasidenib on non-enhancing gliomas was 88% (n=35) (Mellinghoff 2017) and 91% (n=23), respectively (Mellinghoff 2018).

Chondrosarcoma is the most common bone sarcoma in adults and includes several subtypes: conventional, dedifferentiated, mesenchymal, and clear cell. Approximately 85% of all chondrosarcoma cases are of conventional subtype, and another 9% to 10% being dedifferentiated. For primary chondrosarcomas, surgery remains the primary method of treatment; however, there are no standard treatments for advanced disease (Italiano 2013). Chemotherapy is ineffective in conventional chondrosarcoma, and although chemotherapy options exist for dedifferentiated and mesenchymal subtypes, they provide minimal benefit. Recent studies have demonstrated that up to 65% of chondrosarcoma cases harbor an IDH1/IDH2 mutation. In a phase 1 study, ivosidenib, an IDH1 inhibitor, demonstrated a median progression-free survival (PFS) of 5.6 months (95% confidence interval [CI], 1.9-7.4 months) and a PFS rate at 6 months of 39.5% among 21 patients with advanced chondrosarcoma (Tap 2020).

Cholangiocarcinoma refers to malignant tumor originating in the bile duct epithelial cells, accounting for 10% to 15% of all primary liver cancers and less than 1% of all systemic tumors. Prognosis for intrahepatic cholangiocarcinoma is poor, with a 5-year survival rate of only 10%. It is more commonly seen in the 70- to 80-year-old demographics and has a slightly higher incidence rate in males (male:female ratio, 1.2-1.5:1.0). Intrahepatic cholangiocarcinoma arising from the intrahepatic biliary tree accounts for 10% to 20% of cholangiocarcinoma (Valle 2016). About 25% of patients with intrahepatic cholangiocarcinoma have IDH1 mutation (Lowery 2017). In the randomized, phase 3, ClarIDHy study, ivosidenib, an IDH1 inhibitor, demonstrated a median PFS of 2.7 months [95% CI, 1.6-3.6 months] for ivosidenib versus 1.4 months [95% CI, 1.4-2.5 months] for placebo (hazard ratio [HR], 0.47 [95% CI, 0.33-0.68]; p<0.0001). The median overall survival (OS) was 10.8 months (95% CI, 7.7-17.6 months) for the ivosidenib group versus 9.7 months (95% CI, 4.8-12.1 months) for the placebo group (HR, 0.69 [95% CI, 0.44-1.10 months]; p=0.060) (Abou-Alfa 2020).

HMPL-306 is a novel, small-molecule, orally available, highly selective, and potent inhibitor of mIDH. It demonstrated a remarkable inhibitory effect on 2-HG in tumor cells with any IDH mutations, and therefore, this phase 1, open-label study is planned to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutations.

2.2 Background

2.2.1 Description of HMPL-306

HMPL-306 is a highly selective, potent inhibitor that targets mutant IDH1/IDH2, which is characterized by a high oral bioavailability, a low clearance rate, an extensive tissue distribution, a relatively low risk of drug-drug interactions, and satisfactory preclinical safety features. HMPL-306 is available in tablet formulation of 2 strengths: CCI mg and CCI mg.

2.2.2 Supportive Nonclinical Data

2.2.2.1 Pharmacology

Further details on pharmacology are provided in the Investigator's Brochure (IB).

2.2.2.1.1 *In Vitro* Pharmacodynamics

In an *in vitro* enzyme activity study with IDH1 mutation, HMPL-306 showed intermediate inhibitory activity on the IDH1-R132H mutant, which exhibits selectivity compared to its inhibitory activity on wild-type IDH1 enzyme. In the *in vitro* enzyme activity study of IDH2 mutations, HMPL-306 had strong inhibitory activity on IDH2-R140Q and IDH2-R172K mutant enzymes, similar to the activity of positive control compound AG-221 and had high selectivity (~18 times) compared to its inhibitory activity on wild-type IDH2 enzyme. HMPL-306 also significantly inhibits the production of 2-HG in multiple mutant IDH cell lines.

HMPL-306 has CCI effect on CCI or on 322 kinases in the SelectScreen™ platform, showing high kinase selectivity. On the CEREP platform, CCI, HMPL-306 did not show CCI.

2.2.2.1.2 *In Vivo* Pharmacodynamics

Target inhibitory effect of HMPL-306 on 2-HG in U87MG-IDH2R140Q-M31 tumor model

Following CCI dose administration of HMPL-306, the inhibitory effect against 2-HG increased with the dose and drug concentration, showing good PK/PD correlation. The inhibitory effect on 2-HG after administration of HMPL-306 at CCI mg/kg CCI showed that 24 hours after the last dose, HMPL-306's inhibitory rate on 2-HG was maintained at more than 96%, and the inhibitory rate was significantly higher than that after a single dose at the same dosage.

Target Inhibitory effect of HMPL-306 on 2-HG in HT1080-IDH1R132C tumor model

HMPL-306 was administered at CCI mg/kg, and the target inhibition of HMPL-306 on IDH1 mutation was evaluated by measuring changes of 2-HG levels after 2 to 40 hours. The results showed that, at 16 and 24 hours after dosing in all dose groups, the inhibitory rate of HMPL-306 against 2-HG in tumor tissues reached more than 90%. After CCI mg/kg CCI, 2-HG inhibition rate in tumor tissues reached 97%. Compared with the results of CCI mg/kg, its inhibitory effect on the target was stronger with the increase in drug exposure after CCI.

2.2.2.1.3 Safety Pharmacology

The effect of HMPL-306 on hERG potassium channels expressed in transfected human embryonic kidney (HEK293) cells: The IC_{50} of HMPL-306 was CCI μM on hERG potassium channels.

A study on the effect on cardiovascular system: CCI were observed following a single dose of CCI, and CCI mg/kg of HMPL-306 in Beagle dogs. The no observed adverse effect level (NOAEL) of was CCI mg/kg.

A study of the effect on the central nervous system (CNS): CCI following a single dose of CCI and CCI mg/kg of HMPL-306 in Sprague-Dawley rats. The NOAEL for the CNS was CCI mg/kg.

A study on the effect on the respiratory system: CCI following a single dose of CCI, and CCI mg/kg of HMPL-306 Sprague-Dawley rats. The NOAEL was CCI mg/kg.

2.2.2.2 Toxicology

The completed toxicological studies of HMPL-306 included: studies on single-dose toxicity in rats and dogs, 4-week repeated dose toxicity studies with an 8-week recovery period in rats and dogs, and genetic toxicity tests combination study (bacterial response mutation test, chromosome aberration test, *in vivo* micronucleus test).

The results of toxicology tests showed that after HMPL-306 was given to rats and dogs in a single dose, CCI, and the maximum tolerated dose was CCI mg/kg and CCI mg/kg, respectively.

In the repeated-dose toxicity study of rats and dogs, CCI in the two species. In rats, CCI were observed. In rats, the NOAEL of HMPL-306 API was CCI mg/kg and the highest non-severely toxic dose (HNSTD) was CCI mg/kg. CCI were observed in dogs. The NOAEL and HNSTD of HMPL-306

API in dogs were determined to be CCI mg/kg in female dogs and CCI mg/kg in male dogs respectively. The common target organ of rats and dogs was CCI. The changes in the CCI were also observed in the high-dose group of rats at the end of the dosing period. After the 8-week recovery period, except that the CCI in the high-dose female rat group, the other changes mentioned above had recovered.

The results of the CCI

Further details on toxicology are provided in the IB.

2.2.2.3 Pharmacokinetics

HMPL-306 has CCI in rats and dogs, CCI, and CCI; it is widely distributed in rats, with the CCI. The exposure of HMPL-306 in the CCI. The main *in vivo* metabolites in rats were the CCI. HMPL-306 was mainly CCI. Drug interaction of HMPL-306 may come largely from: 1) CCI by HMPL-306; 2) CCI by HMPL-306; 3) The impact of other drugs on the major metabolic enzymes CCI of HMPL-306.

Further details on pharmacokinetics are provided in the IB.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

HMPL-306 is in the early stage of development, and the clinical safety profile has not yet been established, but some potential risks have been observed from nonclinical studies and clinical data from drugs in the same class. Measures for managing these potential risks are as shown in Table 3.

Table 3 Summary of Potential Risks of HMPL-306

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal disorders	CCI was observed in rats with doses up to CCI mg/kg of HMPL-306. Gastrointestinal diseases such as nausea, vomiting, diarrhea, mucositis, constipation, abdominal pain, etc. occurred in clinical studies of both enasidenib and ivosidenib.	General guidance to be provided in the protocol for dose interruption/reduction/discontinuation in response to AEs.
Embryotoxicity	At the present stage, the study of effect of HMPL-306 on embryo development has not been implemented. Enasidenib and ivosidenib were associated with maternal toxicity and adverse embryo-fetal effects in pregnant rats.	Women who are pregnant (pregnancy test is positive before drug administration) or breastfeeding will be excluded from the study. Male with partners of childbearing potential or female subjects of childbearing potential will be required to use effective contraception

Table 3 Summary of Potential Risks of HMPL-306

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		methods. Female subjects of childbearing potential will be tested for pregnancy at every cycle.
Non-infectious leukocytosis	Neutrophil count was seen increased by CCI % in animals administered HMPL-306 (CCI mg/kg/day), and no abnormalities were observed at the end of the recovery period. Non-infectious leukocytosis occurred in clinical trials of both enasidenib and ivosidenib.	Peripheral white blood cell count will be monitored at baseline and during the study at regular intervals, particularly at least once weekly in the first 2 cycles (28 days/cycle) of the initial drug administration. Afterward, it will be monitored once a cycle.
Abnormal hepatic function	In the HMPL-306 high-dose (CCI mg/kg/day) group in rats, the CCI showed a CCI % increase and CCI showed CCI % increase. In clinical trials of both enasidenib and ivosidenib, AEs of abnormal hepatic function occurred, including elevated liver enzymes and elevated bilirubin.	Liver function will be routinely monitored.
Eye disorders	A total of 3 rats in the medium-dose (CCI mg/kg/day) and high-dose (CCI mg/kg/day) groups were found to have CCI . Considering that it is a vital functional organ, ophthalmological examination will be added to the clinical trials.	Ophthalmologic examinations will be performed during the Screening. If the subject has undergone the relevant examinations 60 days before treatment, they will not be required to repeat the test for Screening. After the start of treatment, ocular appearance, and slit lamp examinations will be performed every 3 cycles (ie, Day 1 of Cycles 4, 7, and 10) and during the end of treatment visit. Other ophthalmic examinations will be performed when clinically indicated.
Male reproductive system lesions	In rats given a medium-dose of HMPL-306 (CCI mg/kg/day), CCI In the high-dose (CCI mg/kg/day) group, CCI	Male subjects of childbearing potential will be included only if they agree to use effective contraception methods during the study and within 180 days after the last administration of the study drug.
Pancreatic lesions	CCI was observed in male rats administered with a high-dose of HMPL-306 (CCI mg/kg/day) and was not observed during the recovery period.	Serum lipase and amylase will be monitored.
QTcF Interval Prolongation	The inhibitory rate of the negative reference standard and positive reference standard to the hERG potassium current of HMPL-306	QTcF will be monitored throughout the study, and dose modification guidelines are presented for associated AEs based on CTCAE grading criteria.

Table 3 Summary of Potential Risks of HMPL-306

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	was within acceptable range (IC_{50} was as high as CCI μM). CCI, QTcF interval prolongation has been seen as a class effect with other approved IDH inhibitors and may be seen with HMPL-306.	

AE = adverse event; CTCAE = Common Terminology Criteria of Adverse Events; hERG = human Ether-à-go-go-Related Gene; IC_{50} = half-maximal inhibitory concentration; QTcF = interval from start of the Q wave to the end of the T wave interval corrected for heart rate using Fridericia's formula.

2.3.2 Benefit Assessment

This study will enroll subjects with solid tumors, including glioma, chondrosarcoma, or cholangiocarcinoma. This study provides an opportunity for subjects with glioma, chondrosarcoma, or cholangiocarcinoma to participate in a trial of HMPL-306, a novel agent that targets a mutation that is common among these tumors.

2.3.3 Overall Benefit/Risk Conclusion

At present, there are no IDH1 and/or IDH2 inhibitors approved for treatment of the types of cancers being studied in this clinical trial.

HMPL-306 is a dual inhibitor of IDH1 and IDH2, which, in preclinical studies, has demonstrated similar efficacy to single-target IDH inhibitors (ivosidenib), and may have similar benefit to other IDH1 and/or IDH2 inhibitors in the same class.

Preclinical studies, including toxicology studies, indicate that HMPL-306 is well tolerated.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with HMPL-306 are justified by the anticipated benefits that may be afforded to participants with solid tumors with IDH mutations as defined in Section 5.2.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 4.

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	**Part 1 – Dose Escalation:** To evaluate the safety and tolerability of HMPL-306, thereby determining the RP2D and/or the MTD of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	MTD and/or RP2D Safety including DLTs, TEAEs, SAEs, ECGs, and clinical laboratory abnormalities
	Part 2 – Dose Expansion: To characterize the safety and tolerability of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutation	Safety including TEAEs, SAEs, ECGs, and clinical laboratory abnormalities
	Part 2 – Cohort C-1 Only: To determine the 2-HG concentration in surgically resected tumors following pre-surgical treatment with HMPL-306 when compared to untreated tumors	Observed plasma and tumor concentrations of 2-HG
Secondary	**Part 1 and Part 2:** To assess the preliminary antitumor activity of HMPL-306 in subjects with locally advanced or metastatic solid tumors with *IDH* mutations	ORR, DCR, DoR, TTR, and PFS
	Part 1 and Part 2: To assess the PK of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutation	Observed plasma concentrations and PK parameters of HMPL-306
	Part 1 and Part 2: To assess the PD of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutation	Observed plasma concentrations of 2-HG
	Part 2 – Cohort C-1 Only: To characterize the safety and tolerability of HMPL-306 in subjects with locally advanced or metastatic solid tumors with IDH mutations	Safety including, TEAEs, SAEs, deaths, ECGs, and clinical laboratory abnormalities

Table 4 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Exploratory	**Part 1 and Part 2:** To explore the relationship between HMPL-306 PK exposure and 2-HG levels and percent inhibition	Changes from baseline in tumor markers, correlation with drug exposure, and association with efficacy and safety parameters
	Part 1 and Part 2: To explore the influence of gene abnormalities other than *IDH* mutations on safety, efficacy, PD, and PK	
	Part 1 and Part 2: To assess the potential predictive biomarkers or response or progression though collection of serial ctDNA collection	
	Part 2: To explore the relationship between the changes in the frequency of genetic mutation, efficacy, PK, PD, and safety after HMPL-306 treatment in tumor and plasma	
	Part 2 – To assess the OS in subjects enrolled to expansion Cohorts A, B, and D.	OS

2-HG = 2-hydroxyglutaric acid; ctDNA = circulating tumor DNA; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; IDH = isocitrate dehydrogenase; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PD = pharmacodynamics; PFS = progression-free survival; PK = pharmacokinetics; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment emergent adverse event; TTR = time to response.

4 STUDY PLAN

4.1 Study Design

This is a phase 1, open-label, multicenter study to evaluate the safety and tolerability of HMPL-306 administered orally (PO) in treatment of subjects with locally advanced or metastatic solid tumors with IDH mutation.

The study consists of 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion).

4.1.1 Part 1 (Dose Escalation)

The first part of the study is dose escalation where cohorts of subjects will receive ascending oral doses of HMPL-306 to determine maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D). The modified toxicity probability interval-2 (mTPI-2) (Yang 2015) design will be utilized for dose escalation until determination of MTD/RP2D. The mTPI-2 method uses a Bayesian framework and a hierarchical model to compute the dose escalation based on the interval between the toxicity rate of each dose level and target probability (Guo 2017). This study is designed targeting a dose-limiting toxicity (DLT) rate of 25% with an equivalence interval of 20% to 30%.

Like the 3+3 design, the mTPI-2 method incorporates pre-specified escalation rules that can be presented in a table (Table 6). As shown in Table 6, the number of subjects dosed at a given dose level is shown in the columns, while the rows indicate the number of DLTs experienced. The escalation/de-escalation rules from the table will be used for each dose level evaluated; the subject numbers and DLTs do not carry over from cohort to cohort. As an example, within a cohort:

- If none of the 3 subjects experience a DLT → escalate the dose ("E" at column 3 row 0) to the next dose level cohort
- If 1 out of 4 subjects experience a DLT → stay at the same dose level ("S" in column 4 row 1)
- If 2 out 3 subjects experience a DLT → de-escalate to a lower dose level ("D" at column 3 row 2)
- If 3 out of 3 subjects experience a DLT → the dose is determined to be unacceptably toxic and will not be used again, de-escalate to a lower dose level ("DU" at column 3 row 3)

The following rules apply during dose escalation:

- The initial dose will be [redacted] mg PO, once a day (QD)
- Although in the mTPI-2 method the cohort size is not fixed, at least 3 subjects will be enrolled at each dose level. When all subjects at a dose level complete DLT assessment, the study will escalate to the next dose level and another 3 subjects will be recruited in the order of dose escalation plan until RP2D or MTD Table 6. A minimum of 3 subjects will be enrolled in each cohort.
- The sample size of a dose cohort that has already passed the preliminary DLT assessment (1 to 3 subjects) and has shown efficacy can be extended to 12 cases in order to further evaluate the safety and efficacy signals of this dose
- The study stage will prematurely end when any of the following conditions are met:

- Excessive toxicity is present in the initial dose
- Although no excessive toxicity is present in the first dose level cohort, if the dose returns to the initial dose according to the rules in Table 6 and excessive toxicity is present at the initial dose (for example, 4 or more DLTs are observed in 6 subjects)

Please see Section CCI .

A cycle of study treatment is defined as 28 days of continuous daily dosing, according to the cohort and dose level. At the starting dose, subjects will be administered HMPL-306 at CCI mg PO, QD, and the dose will escalate successively according to the sequence of CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, and CCI mg QD. (see Table 5). The modified Fibonacci design will be used to escalate the dose (see Table 6 for details on the dose escalation decision).

The addition of dose levels 5 to 8 in Protocol Amendment 2 is based on the cumulative safety and preliminary PK and PD data review conducted by the Sponsor and the Safety Review Committee (SRC) members. Following completion of enrollment of dose levels 1 to 4, the PD data reviewed did not demonstrate the desired level of 2-HG inhibition for the Sponsor and the SRC members to declare the RP2D to move to Part 2. Pharmacokinetic data review showed dose proportional increase in PK exposure over the dose range of CCI mg to CCI mg QD. As there were no DLTs or safety concerns noted in dose levels 1 to 4, the Sponsor and SRC members agreed to continue escalation at higher dose levels.

Table 5 Subject Dose Grouping (Dose Escalation Plan)

Dose Level	Dose of HMPL-306 PO, QD[a] with water
1	CCI mg
2	mg
3	mg
4	mg
5	mg
6	mg
7	mg
8	mg

PO = orally; QD = once a day.

Table 6 mTPI-2 Decision Table for Dose Selection

Target toxicity probability (pT)=25%; ε1=0.05; ε2=0.05

Number of Patients with DLTs \ Number of Patients	1	2	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	S	S	E	E	E	E	E	E	E
2		DU*	D	D	D	D	S	S	S	S	E	E
3			DU	DU	DU	D	D	D	D	D	S	S
4				DU	DU	DU	DU	DU	D	D	D	D
5					DU	DU	DU	DU	DU	DU	D	D
6						DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU
9									DU	DU	DU	DU
10										DU	DU	DU
11											DU	DU
12												DU

E=increased to the next higher dose; D=reduced to a previous lower dose; DLT=dose-limiting toxicity; DU=reduced to a previous lower dose and the current dose will not be used again in this trial; MTD=maximum tolerated dose; mTPI-2=modified toxicity probability interval-2; pT=toxicity probability; S=maintaining the same dose.

*If 2 out of 2 subjects have DLTs when treated at the lowest dose level, the Sponsor, based on recommendations from the Safety Review Committee (SRC), can choose to terminate the study or to enroll 1 more subject.

Note: The horizontal axis indicates the number of subjects who are treated at the current dose, and the longitudinal axis is the number of subjects observed with DLTs. ε1 and ε2 are fractions used to define an equivalence interval of the MTD.

Safety Review Committee

Safety monitoring and evaluation of dose escalation will be carried out by the SRC, which is comprised of the Sponsor and 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 determine the RP2D based on the risk-benefit evaluation.

Dose -Limiting Toxicity

DLT is defined as the occurrence of any of the treatment-emergent adverse events (TEAEs) described in Section 8.1.3 during the DLT assessment window, unless the TEAEs are clearly unrelated to the study drug or judged by the investigator as not clinically significant.

DLT Assessment Window:

For all subjects in dose escalation, DLTs will be assessed during the DLT assessment window of 28 days (Cycle 1 Day 1 [C1D1] through C1D28).

DLT-Evaluable Subject:

A subject is DLT evaluable if the following criteria are met:

- Has received at least 75% of the assigned dose of study medication during the DLT assessment window

  OR

- Has not completed the DLT assessment period due to a DLT

For decisions on dose escalation, each dose cohort shall present protocol-required numbers of DLT-evaluable subjects. Subjects who are not DLT evaluable in a dose cohort will be replaced to guarantee the protocol-required numbers of DLT-evaluable subjects for dose escalation evaluations.

Subjects who complete the DLT assessment window and are deemed by the investigator to be benefiting from HMPL-306 treatment will be allowed to continue treatment until disease progression, intolerable toxicity, at the investigator's discretion that the subject can no longer benefit from the study treatment, withdrawal of consent, lost to follow-up, the end of study, or death, whichever comes first.

Maximum Tolerated Dose

The MTD determination will be driven by the mTPI-2 method, and as such, the MTD will be any doses with true toxicity probability in the equivalence interval. For this study, the equivalence interval is defined as 20% to 30%.

Recommended Phase 2 Dose

RP2D determination will take the following criteria under consideration:

- Determination of MTD achieved during the dose escalation part
- Assessment of safety, PK, and PD

4.1.2 Part 2 (Dose Expansion)

In the dose expansion part, 4 cohorts of subjects will receive HMPL-306 to further evaluate the safety, tolerability, PK, PD, and preliminary efficacy of HMPL-306 at MTD or RP2D in approximately 95 subjects with locally advanced or metastatic solid tumors with IDH mutations.

There will be approximately 20 subjects (15 subjects in Cohort C-1) in each of the following cohorts:

- **Cohort A:** Cholangiocarcinoma
- **Cohort B:** Skeletal chondrosarcoma
- **Cohort C:** Low-grade glioma
  - **Cohort C-1:** Perioperative glioma
- **Cohort D:** Any other solid tumor harboring an IDH mutation

Depending on preliminary efficacy, safety signals, or operational feasibility, the Sponsor in conjunction with the SRC may decide to reduce or increase enrollment in these cohorts.

Study Treatment

Subjects will receive HMPL-306 at MTD or RP2D for 28 days in each cycle until disease progression, death, intolerable toxicity, the investigator's judgement that the subject can no longer benefit from the study treatment, withdrawal of consent, loss to follow-up, death, or the end of the study, whichever occurs first.

Cohort C-1: Perioperative Glioma

This cohort will serve as an open-label, window of opportunity study to assess the concentration of 2-HG in surgically resected tumors following pre-surgical treatment with HMPL-306 when compared to untreated tumors. This cohort will enroll 15 subjects with recurrent low-grade glioma with IDH1 or IDH2 mutations who are candidates for surgical resection. Subjects will be randomized in a 2:1 fashion to receive either open-label HMPL-306 at the RP2D for 4 weeks prior to surgery or no treatment (control) for 4 weeks prior to surgery.

All subjects enrolled to this cohort will undergo pre- and post-treatment procedures as outlined in Table 2. All subjects will have the option of receiving HMPL-306 following surgery. Subjects with no residual disease following surgery will be allowed to receive HMPL-306 for up to 1 year or until disease progression, whichever occurs first. If residual disease is evident following surgery, those subjects may receive HMPL-306 until disease progression.

4.2 Design Rationale

4.2.1 Rationale for Starting Dose and Dosing Regimen

HMPL-306 is intended for use in subjects with advanced solid tumors. Hence, the starting dose is calculated based on the S9 guidelines from International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, using the HNSTD and no-observed-adverse-effect level dose. According to the HNSTD of the repeated dose toxicology study of rats and dogs, the safe doses obtained based on the equivalent area in human are CCI mg/day and CCI mg/day, respectively. In accordance with ICH S9, the initial dose for the first-in-human (FIH) study should be 1/10 of the HNSTD in rats or 1/6 of the HNSTD in dogs. Consequently, the starting dose calculated for FIH study should be CCI mg/day. Further, the nude mouse PD test showed that CCI mg/day is the clinical dose that is likely to have an effect in humans based on the equivalent skin surface area in human. Based on the aforementioned study results and calculations, the initial dose for this FIH phase 1 clinical trial is CCI mg/day. Therefore, the safety window is more than 14 times and about 78 times as calculated, according to study results in rats and dogs, respectively. It is also inadvisable to intentionally provide an ineffective treatment dose for a long time to subjects with cancer with intractable disease.

Furthermore, according to ICH S9, the dosing interval for the FIH study should be based on the dosing interval used in the preclinical toxicity study for continuous dosing and half-life in the test species. The dosing interval of HMPL-306 in the 4-week repeated dose toxicity study in animals was once daily. The half-life was CCI hours in rats and CCI hours in dogs. Therefore, the regimen of once daily dosing will be first explored in this phase 1 study. Nevertheless, if other dosing frequency is necessitated, then the investigator and the Sponsor will discuss and make a collective decision regarding the dosage regimen going forward in the clinical study. The decision will be based on the evaluation of clinical data available at that time, particularly the pharmacometric/PK data.

4.2.2 Rationale for Study Population Selection

IDH1 or IDH2 mutations have been identified as driver mutations leading to the proliferation and metastasis across various tumor types. Solid tumors such as cholangiocarcinoma, skeletal chondrosarcoma, and low-grade glioma have been identified as tumor types with a high prevalence of IDH1 and/or IDH2 mutations, making them good clinical candidates for treatment with an IDH1 and/or IDH2 inhibitor. Thus, this study plans to enroll the aforementioned population to assess the safety, tolerability, and preliminary efficacy of HMPL-306 treatment.

Additional discussion of rationale for including specific tumor types with a high prevalence of IDH1 and/or IDH2 mutations, and line of therapy can be found in Appendix 11.

4.2.3 Rationale for Biomarker Testing

As a highly selective inhibitor of mutant IDH1R132H/C, IDH2R140Q, and IDH2R172K, HMPL-306 has the potential to play a crucial role in the treatment of subjects with solid tumors with any of these IDH mutations. Consequently, this study will conduct testing for IDH mutations and enroll subjects with any IDH mutations or any combinations thereof.

Based on available data from development experience of IDH inhibitors on the market, the mutation of CCI that coexist with mutant IDH1 may affect the efficacy of IDH1 inhibitor ivosidenib. Clinical studies of IDH2 inhibitor enasidenib also found that overall response was worse in subjects with aberration of CCI This suggests that testing for other gene co-mutations that coexist with mutant IDH is helpful to retrospectively analyze the efficacy of HMPL-306 in these subjects. Therefore, at baseline (before the start of treatment), circulating tumor DNA (ctDNA) blood samples are collected to test for full spectrum of possible gene mutations. This has the potential to reveal gene mutations and co-mutations that co-exist in subjects having clinical benefits from antitumor activity of HMPL-306.

CCI and CCI may be one of the main metabolic enzymes for in vivo metabolism of HMPL-306. The mutation of CCI and CCI may have an impact on PK parameters of HMPL-306, which may further affect the efficacy and safety of the investigational product (IP). Therefore, there is the necessity for collection of blood samples at baseline for CCI and CCI genetic testing.

2-HG is a tumor metabolite produced by mutant IDH enzyme-catalyzed substrate α-KG. The changes in the blood levels of 2-HG and that in tumor tissue, if available, are helpful to determine the degree of target inhibition provided by the HMPL-306 as an indicator of PD effectiveness. This study will monitor the changes in the levels of 2-HG in blood in all cohorts and glioma tissue in Cohort C-1. In this way, the mechanism of action of HMPL-306 can be verified to evaluate its correlation with the efficacy of the IP.

Progressive disease is often associated with new mutations or co-mutations or changes (upregulation) in the expression of current mutant gene. In this study, blood samples containing ctDNA will be collected to monitor changes in the levels of full spectrum of possible gene mutations or co-mutations associated with all tumor types under study. This is to explore all possible biomarkers and their expression levels in correlation with the efficacy of HMPL-306, as well as potential mechanism of drug resistance.

5 POPULATION

5.1 Definitions

Subjects officially enter the Screening Period following the provision of informed consent either directly or via a legally authorized representative where it is permitted by local law.

Pre-screening failure refers to subjects who have signed pre-screening informed consent but are tested negative for any IDH mutations or have withdrawn consent. Subjects who fail pre-screening will have the following information recorded: demographic information, disease diagnosis, IDH mutations status, and reason for pre-screening failure.

A screen failure is a consented subject who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may be rescreened. However, before informed consent is obtained, if the assessments for standard treatment are performed within 28 days before the planned C1D1, they can be used to replace the assessments during the Screening Period without repeating the assessments, except for assessments that need to be performed 7 days before the start of the study drug administration, as specified in Table 1 and Table 2. If there is dosing on the assessment day, all assessments should be completed before the study drug administration, except for 12-lead electrocardiogram (ECG), echocardiogram (ECHO)/multigated acquisition (MUGA) scan, ophthalmologic assessments, and efficacy assessments.

An enrolled subject is one who has been deemed eligible and has been assigned to a treatment group.

Inclusion/exclusion waivers will not be granted.

5.2 Inclusion Criteria

Subjects may be enrolled in this study only if they satisfy all the following criteria:

1. Subjects must be ≥18 years of age.
2. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1.
3. Subjects must have a measurable or evaluable disease for Part 1 (Dose Escalation) and subjects must have a measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (or Response Assessment in Neuro-Oncology [RANO] criteria for gliomas) for Part 2 (Dose Expansion).
4. Subjects must have an absolute neutrophil count (ANC) of $\geq 1.5\times10^9$/L, platelet count of $\geq 75\times10^9$/L, and hemoglobin of ≥8 g/dL.
5. Subjects must have adequate hepatic function as evidenced by the following: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3× upper limit of normal (ULN), except for subjects with liver metastasis who are included if ≤5× ULN and total bilirubin ≤1.5× ULN.
6. Subjects must have serum albumin ≥2.8 g/dL.
7. Subjects must have creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault formula.

8. Subjects must have an international normalized ratio (INR) of ≤1.5 or an activated partial thromboplastin time (aPTT) of ≤1.5× ULN.
9. Subjects must be recovered to ≤Grade 1 from all toxic effects of any prior surgery, radiotherapy, or other therapy.
10. Subjects must have recovered from surgery, at least 2 weeks post-surgery prior to starting study drug.
11. For gliomas (Part 1, and Cohort C), subjects must not show enhancing disease on T1-gadolinium-magnetic resonance imaging (Gd MRI).
12. Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days of study drug administration. NOTE: Postmenopausal is defined as ≥24 months of amenorrhea and at least 50 years of age.
13. Female subjects of childbearing potential and male subjects with partners of childbearing potential must 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 180 days after taking the last dose of study drug. Such methods include oral hormonal contraception (combined estrogen/progestogen or progestogen-only) 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 subjects involved in this clinical trial if they have a partner of childbirth potential, and male subjects must always use a condom.

Part 1, Dose Escalation:

14. Subjects must have a documented IDH mutation per immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) testing of tumor tissue.
15. Subjects must have histologically or cytologically documented, locally advanced or metastatic solid malignancy of any type that has recurred or progressed on available standard treatment and for which no curative therapy exists.
    a. Subjects with Grade 3 non-enhancing glioma are permitted to enroll to Part 1.

Part 2, Dose Expansion:

16. Subjects in Cohorts A, B, C, C-1, and D must have documented IDH mutation of any of the following subsets: IDH1 (R132), IDH2 (R140), or IDH2 (R172), including any co-mutations, per validated NGS testing of tumor tissue
17. Subjects must have histologically or cytologically documented:
    b. **Cohort A:** Locally advanced or metastatic cholangiocarcinoma not eligible for curative resection or transplantation. Subjects must have previously received

≥1 gemcitabine- or 5-fluorouracil-containing regimen. Subjects must have not progressed on prior IDH treatment unless isoform switching of the IDH mutation has been documented following progression on an IDH inhibitor

c. **Cohort B:** Locally advanced or metastatic skeletal chondrosarcoma. Subjects must have not progressed on prior IDH treatment unless isoform switching of the IDH mutation is documented following progression on an IDH inhibitor

d. **Cohort C:** Recurrent Grade 2 gliomas that are not a candidate for clinical resection. Progression or recurrence must have occurred ≤12 months prior to study enrollment. Subjects must have not progressed on prior IDH treatment unless isoform switching of the IDH

e. **Cohort C-1:** Subjects with recurrent Grades 2 and 3 gliomas who are candidates for clinical resection but for whom surgery is not urgently indicated. Subjects must not have received prior treatment with an IDH inhibitor

f. **Cohort D:** Any other locally advanced or metastatic solid tumor harboring an IDH mutation that has progressed on at least 1 line of prior therapy. Subjects must have not progressed on prior IDH treatment unless isoform switching of the IDH mutation is documented following progression on an IDH inhibitor

5.3 Exclusion Criteria

Subjects are not eligible for enrollment into this study if they meet any of the following criteria:

1. Subjects who received systemic anticancer therapy or radiotherapy <14 days prior to their first day of study drug administration (radiotherapy <12 weeks for glioma subjects)
2. Subjects who received an investigational agent <14 days prior to their first day of study drug administration
3. Subjects who are pregnant or breastfeeding
4. Subjects with an active severe infection or with an unexplained fever >38.5°C during screening visits or on their first day of study drug administration (at the discretion of the investigator, subjects with infection that is controlled with appropriate therapy are eligible)

   a. See Appendix 10 for procedures specific to subjects with suspected or confirmed coronavirus disease 2019 (COVID-19)

5. Subjects with New York Heart Association (NYHA) Class III or IV congestive heart failure or left ventricular ejection fraction <40% by ECHO or MUGA scan within approximately 28 days of C1D1 (Appendix 5)
6. Subjects with a known history of myocardial infarction within 6 months of the first dose
7. Subjects with a known unstable or uncontrolled angina pectoris
8. Subjects with clinically significant or severe gastrointestinal disease or condition that the investigators suspect may affect drug absorption, including, but not limited to, active gastric and duodenal ulcers, ulcerative colitis and other digestive disease, gastrointestinal

tumor with active bleeding, or other gastrointestinal conditions that may cause bleeding or perforation, by investigator's discretion

9. Subjects with a known history of severe and/or uncontrolled ventricular arrhythmias
10. Subjects with interval from the start of the Q wave to the end of the T wave (QT) corrected for heart rate using Fridericia's formula (QTcF) interval ≥470 ms or other factors that increase the risk of QT prolongation or arrhythmic events
11. Subjects taking medications that are known to prolong the QT interval (including, but not limited to, the list in Appendix 4). NOTE: Subjects may participate if medications are changed to acceptable alternatives
12. Subjects taking medications that can CCI (Appendix 6) within 1 week or 5 half-lives (whichever is longer) from the start of study treatment
13. Subjects who receive small-molecule or large-molecule (such as antibody-based drug) drugs in previous clinical studies for <2 weeks or <4 weeks, respectively, from the time of the start of study treatment to the last use
14. Subjects with known infection with human immunodeficiency virus (HIV) or active hepatitis B virus (HBV) or hepatitis C virus (HCV). Screening not required unless subject has clinical findings suggestive of infection with HIV, or HBV or HCV
15. Subjects with brain metastases that are untreated or symptomatic or that require therapy to control symptoms, or any radiation, surgery, or other therapy (including those used to control symptoms) within 4 weeks of the first dose. Subjects with glioma who are on a stable, steroid-dosing regimen at the time of Screening may be permitted to enroll with the Sponsor's approval
16. Subjects with a clinically significant liver disease or condition such as Gilbert syndrome and that, at the discretion of the investigator, may affect drug metabolism
17. **Dose Expansion Only:** Progression on a prior IDH inhibitor treatment unless isoform switching of the IDH mutation is documented following progression on an IDH inhibitor
    a. Subjects in cohort C-1 must not have received treatment with an IDH inhibitor
18. Subjects with a known hypersensitivity to HMPL-306 or to any of its excipients

6 STUDY CONDUCT

Recruitment period is estimated to take approximately 18 months. Estimated duration for the entire study from the time the study is open to enrollment until completion of data analyses is approximately 42 months. During the study, assessments at each study visit will be performed as listed in Table 1 and Table 2, as described in this section.

6.1 Study Procedures

6.1.1 Pre-Screening Period

Pre-screening period is defined from signing of pre-screening informed consent to obtaining IDH mutational status report or withdrawal of consent. Subjects who have already tested positive for IDH mutation may enter the Screening period directly.

6.1.2 Screening Period

The Screening period is defined as the period from the Screening visit to before the first dose of HMPL-306 administration (up to 28 days prior to C1D1).

6.1.3 Treatment Period

The treatment period is defined as the time from HMPL-306 administration on C1D1 to end-of treatment (EOT) visit.

6.1.4 Medical History and Demographic Information

Medical history data include significant clinical disease or symptom, surgical history, history of malignancy (including date of diagnosis; classification and prognosis evaluation of the study disease, the treatment performed, and the outcome; and the tumor type and outcomes of any other previous malignancies), smoking history, history of alcohol consumption, history of drug abuse, and other medical-related history. Prognosis evaluation of the study disease will be performed according to the RECIST Version 1.1 (Appendix 8) or RANO for gliomas (Appendix 9).

Demographic information includes sex, race, and in some countries, year of birth should be recorded at Screening and in the applicable electronic case report form (eCRF) as permitted by local regulations.

6.1.5 Prior and Concomitant Medications and Concomitant Procedures

Concomitant medications include any prescription and over-the-counter medications. During the Screening Period, all drugs used by the subject within 28 days prior to the start of HMPL-306 administration should be recorded in the eCRF. In subsequent visits, the drugs used by that period and within 30 days after termination of treatment should be recorded in the eCRF. Subsequent new antitumor treatment regimens during the Safety and Efficacy Follow-up Periods will also be recorded. Concomitant medications should be reviewed during the study according to the schedule in Table 1 and Table 2.

6.1.6 Vital Signs

Vital signs include blood pressure, body temperature, heart rate, and respiratory rate. Vital signs should be assessed during the study according to the schedule in Table 1 and Table 2.

6.1.7 Physical Examination, Weight, and Height

Physical examination and weight measurement will be conducted during the study according to the schedule in Table 1 and Table 2. Physical examination includes the examination of the head, neck, ears, nose, eyes, throat, skin and mucous membranes, and gastrointestinal tract, as well as cardiovascular, renal, skeletal, muscular, respiratory, and nervous systems.

Height will only be measured during the Screening Period.

6.1.8 ECOG Performance Status

ECOG PS scoring will be performed during the study according to the schedule in Table 1 and Table 2. Performance status will be carefully scored in strict accordance with the criteria (Appendix 3), especially to determine eligibility for enrollment.

6.1.9 Ophthalmologic Assessments

Ophthalmologic assessments, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, optical coherence tomography, and intraocular pressure, will be performed during the study according to the schedule in Table 1 and Table 2. If the subject has undergone the relevant examinations 60 days before the start of IP treatment (C1D1), they need not be repeated. Other ophthalmic examinations are to be performed when clinically indicated. If the subject develops an ophthalmic AE related to HMPL-306, the frequency of the examination should be increased to once every cycle until the AE is relieved or stable.

6.1.10 Laboratory Evaluations

Assessments will be performed in the laboratories of the respective study site to monitor. The range of normal values of all study sites will be collected prior to the start of the study.

6.1.10.1 Hematology

Hematology, including red blood cell count, hemoglobin, hematocrit, white blood cell count with differential and classifications (neutrophils [ANC and neutrophils %], lymphocytes [absolute lymphocyte count and lymphocytes %], eosinophils [absolute eosinophil count and eosinophils %], monocytes [absolute monocyte count and monocytes %], and basophils [absolute basophil count and basophils %]), and platelet count, will be performed during the study according to the schedule in Table 1 and Table 2. If abnormal or primitive immature cells are seen, they will also be recorded. Any additional routine blood tests during the study shall be arranged by the investigator as needed.

6.1.10.2 Blood Chemistry

Blood chemistry, including blood urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, blood glucose, creatine phosphokinase, total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, lactate dehydrogenase, total protein, and albumin, will be performed during the study according to the schedule in Table 1 and Table 2.

6.1.10.3 Blood Amylase and Lipase

Tests for blood amylase and lipase will be performed during the study according to the schedule in Table 1 and Table 2.

6.1.10.4 Fasting Lipid Panel

Fasting lipid panel, including total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides, will be performed during the study according to the schedule in Table 1 and Table 2.

6.1.10.5 Coagulation Indicators

Tests for coagulation indicators, including prothrombin time, aPTT, and INR, will be performed during the study according to the schedule in Table 1 and Table 2.

6.1.10.6 Glycated Hemoglobin

Tests for glycated hemoglobin (HbA1C) will be performed as per schedule in Table 1 and Table 2.

6.1.10.7 Serum Pregnancy Test

Female subjects of childbearing potential (including those who have undergone tubal ligation) must undergo a serum pregnancy test within 7 days of study drug administration and record a negative result. After enrollment, serum or urine pregnancy test should be conducted according to the schedule in Table 1 and Table 2. Unscheduled testing can be performed if there is an indication.

6.1.10.8 Urinalysis

Urinalysis (or dipstick), including glucose, protein, ketone body, red blood cells, white blood cells, and urobilinogen, will be performed during the study according to the schedule in Table 1 and Table 2.

6.1.10.9 Virological Screening

Virological screening is only required if subject has finding suggestive of active viral infection and includes HIV, HBV (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B e-antigen [HBeAg], hepatitis B e-antibody [HBeAb], and hepatitis B core antibody [HBcAb]), cytomegalovirus (CMV antibody), and HCV (HCV antibody). If HBsAg or HBcAb or CMV antibody is positive, CMV DNA or HBV DNA is also required to be assayed by PCR method. If CMV DNA or HBV DNA is negative, subjects may be enrolled and their CMV DNA or HBV DNA should be monitored every cycle. If HCV antibody is positive, HCV RNA is required to undergo PCR testing. Virological screening will be performed during the Screening Period.

6.1.10.10 IDH Mutational Status

Subjects who have reports of positive IDH mutation status may directly enter the Screening phase without pre-screening. Information regarding test methodology will be collected for subjects in Part 1. Subjects who have not been tested for IDH mutations should be tested locally (via biopsy tissue collection) at the clinical trial site to determine IDH mutation status before enrollment.

Subjects will be required to provide samples for IDH mutational status confirmation as outlined in Section 6.1.14.

6.1.11 Electrocardiogram

The 12-lead ECG indicators include PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate. Evaluation time points are shown in Appendix 1 and Appendix 2. Unscheduled ECG or other cardiac examinations can be performed if clinically indicated.

6.1.12 Echocardiogram/Multigated Acquisition Scan

To evaluate the ejection fraction of subjects, ECHO (preferred method) or MUGA scan will be performed during the study according to the schedule in Table 1 and Table 2. It is recommended to use the same assessment method throughout the study for each subject.

6.1.13 Tumor Assessment

Tumor time point response assessment will be performed by the investigators according to RECIST Version 1.1 (Appendix 8) or RANO criteria for glioma subjects (Appendix 9). The tumor assessments will be performed during screening, every 8 weeks (±1 week) beginning on C1D1 for the first 24 weeks , and every 12 weeks (±2 weeks) thereafter as specified in Table 1 and Table 2, through EOT or end of Efficacy Follow-up (if applicable).

All measurable and evaluable lesions should be assessed and documented using image-based evaluation. All subjects are to be evaluated utilizing contrast-enhanced computed tomography (CT) scan or positron emission tomography (PET) scan or Gd MRI for glioma subjects to identify and follow selected lesions throughout the study. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement.

Tumor assessments completed as standard of care prior to signing of the informed consent but, within 28 days of first dose of study treatment, may be used as baseline scans. Assessments throughout the study should be made using the same modality as used at Screening.

6.1.14 IDH Mutation Confirmation

Samples will be collected for central confirmation of IDH mutation status in order to validate local results or reports used by sites to determine eligibility for trial. Collected samples will follow specified procedures as indicated in the laboratory manual. If archival tissue is not available, a fresh tissue biopsy will be required. This independent confirmation will use NGS, performed at a central laboratory at pre-specified intervals as determined by the Sponsor. All samples should be prepared, labeled, handled, packaged, stored, and transported in accordance with required processes as provided in the study-specific laboratory manual.

6.1.15 Pharmacokinetics and Pharmacodynamic Evaluation

6.1.15.1 Sample Collection and Handling

Blood samples will be collected for PK and PD analysis of HMPL-306 and 2-HG levels in plasma, respectively. For Cohort C-1, glioma samples will be collected during surgery for the analysis of 2-HG and HMPL-306 levels. The full PK and PD evaluation schedule is presented in Appendix 1

and in Appendix 2 for Cohort C-1. Patients enrolled to the control arm of Cohort C-1 will not need to undergo PK sampling in the pre-surgery period of the study.

The collection, handling, and transportation of biological samples should be carried out in accordance with the requirements in the study-specific laboratory manual.

6.1.15.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of HMPL-306 and 2-HG using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC MS/MS) method. Glioma tissue samples will be analyzed to determine concentrations of HMPL-306 and 2-HG using a qualified method.

Plasma samples may also be analyzed to document the presence of circulating metabolites using a qualified research method. If conducted, metabolite analysis will be reported outside of the clinical study report.

6.1.16 Exploratory Biomarker Evaluation in Tumor Specimen

Biomarkers related to HMPL-306 and solid tumors will be explored to analyze the possible correlation between biomarkers and clinical results.

Tumor tissue will be collected according to the schedule in Table 1 and Table 2. In the expansion part, for subjects participating in the exploratory portion of the study, at disease progression during HMPL-306 treatment or EOT, tumor tissues (formalin-fixed paraffin-embedded samples; block or 10 unstained slides, minimum tissue area, 25 mm^2) will be collected to check IDH mutation status and other co-occurring gene alterations to explore the resistance mechanism of HMPL-306. For Cohort C-1, the tumor samples collected during the surgery will also be used to assess the molecular and cellular changes if the remaining sample is available after PK/PD study.

All tests are completed by the central laboratory, and all samples should be prepared, labeled, and transported according to the requirements in the study-specific laboratory manual.

6.1.17 Circulating Tumor DNA

Blood samples including ctDNA will be collected according to the schedule in Appendix 1 and Appendix 2. ctDNA samples will be collected at the escalation and expansion part for tumor somatic mutations (eg, CCI [redacted], etc) detection. For collection and shipping instructions, please refer to the study-specific laboratory manual. The dates of blood sampling must be recorded in the eCRF.

6.1.18 Lifestyle Management

Subjects enrolled in this study are advised to avoid unnecessary exposure to sunlight or any other source of ultraviolet light during their participation in the study and until 30 days after their last dose of study drug. Subjects are encouraged to wear sunglasses and apply sunscreen products with protective coefficient of at least SPF 15 as necessary. The safety risks of HMPL-306 under sunlight are not yet clear, and further nonclinical studies are planned to assess its photo-toxicity effects of HMPL-306.

6.1.19 End of Treatment Visit

Subjects who have completed the study or have discontinued study treatment will be asked to return to the investigational site to receive safety examinations and assessments within 7 (±3) days after the last dose of study drug**.**

6.1.20 Follow-up Period

Safety Follow-up

Subjects who have completed the study treatment will be evaluated for safety 30 days (±7) days following the EOT visit for study drug-related AEs until resolution and SAEs until resolution regardless of relationship to study treatment.

Efficacy Follow-up

Subjects who discontinue the study drug due to reasons other than disease progression, death, lost to follow-up, or withdrawal of consent will remain on study and will be followed every 12 weeks (±14 days) from EOT visit for tumor assessment until disease progression, initiation of new anticancer therapy, withdrawal of consent, lost to follow-up, death, or the end of the study, whichever comes first.

Survival Follow-up

All subjects in expansion cohorts A, B, and D may be followed for survival status every 12 weeks (±14 days), for a maximum of 2 years from EOT visit until death, lost to follow-up, or withdrawal of consent. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

6.1.21 End of Study

The end of the study is defined as the date on which all subjects have their last visit or 1 year after the last subject has their first visit, whichever comes first.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Subjects

6.2.1.1 Permanent Discontinuation of Treatment

The investigator has the right to discontinue a subject from the study for any medical condition that the investigator determines is in the best interest of the subject, reasons of non-compliance (eg, missed doses, visits), or pregnancy.

Any subject who discontinues treatment should be encouraged to return to the study site for an EOT visit and continue with the remaining study visits outlined in Table 1 and Table 2. The primary reason for discontinuation must be recorded on the appropriate eCRF.

Subjects must be discontinued from treatment for any of the following reasons:

1. Disease progression. If the subject is experiencing a treatment benefit, in the opinion of the investigator, the subject may continue study drug beyond radiographic progression until clinical progression. Determination of clinical progression is at the discretion of the

investigator and may include both objective and subjective data. The continuation decision should be made by the investigator in consultation with the Sponsor

2. Withdrawal of consent
3. Intolerable toxicity or AEs that warrant withdrawal of study treatment as determined by the principal investigator or as outlined in Section 7.4.2.
4. Poor subject compliance
5. Use of other antitumor treatment during the study
6. Pregnancy
7. Subject is lost to follow-up
8. The investigator or the Sponsor determines it is in the best interest of the subject
9. Study is terminated by the Sponsor
10. Death
11. End of this study

6.2.1.2 Withdrawal from Study

All subjects have the right to withdraw from the study at any time. During the treatment period and follow-up period, a subject who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn. Every effort should be made to obtain information on subjects who discontinue study drug but who do not withdraw consent to continue participation in the study. If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

All subjects who withdraw from the study may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.2.1.3 Replacement of Subjects

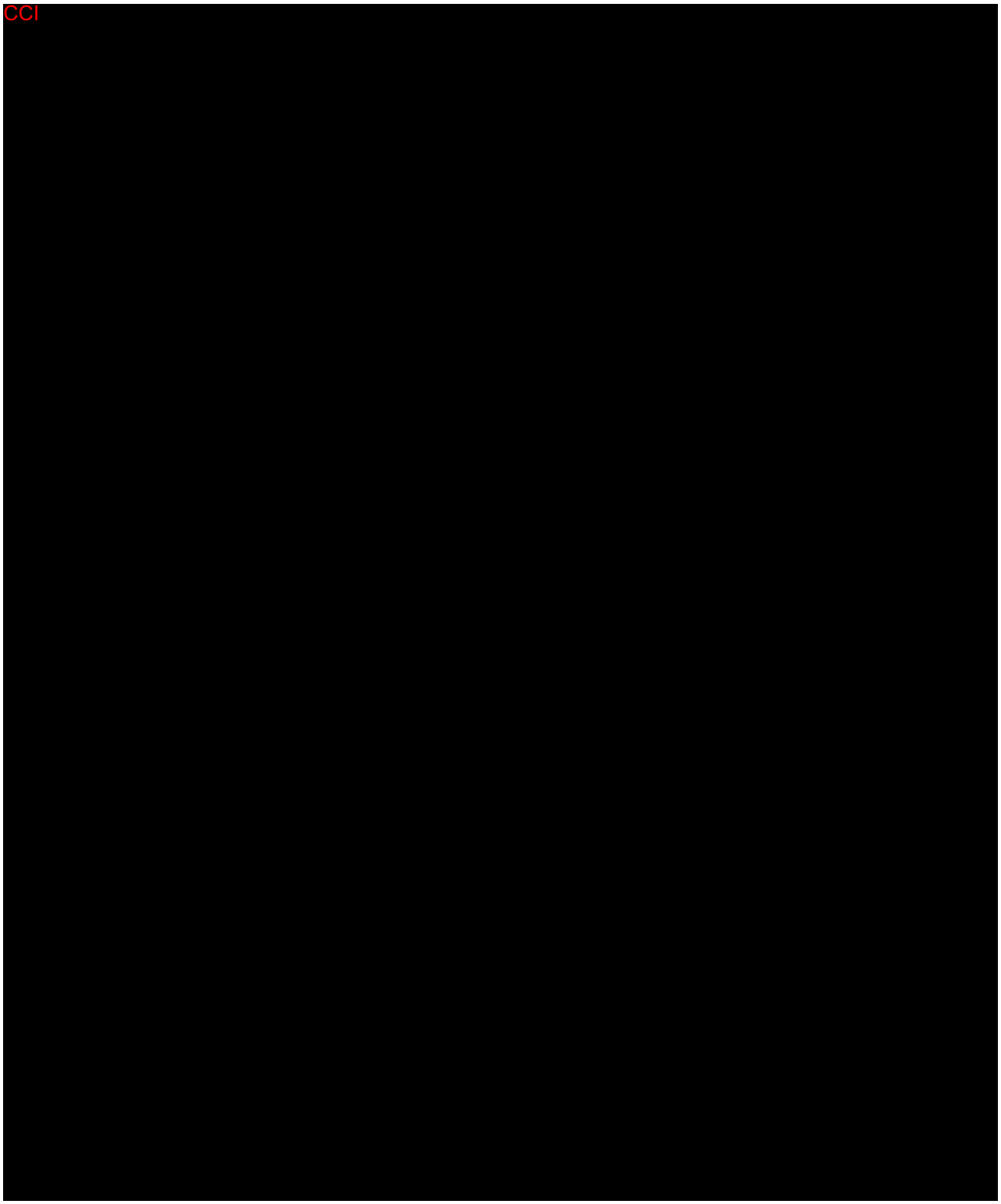
Subjects who are not DLT evaluable in a dose cohort will be replaced to guarantee the protocol-required number of DLT-evaluable subjects for dose escalation evaluations. Subjects who are not eligible for response assessment (defined as those subjects who completed a follow-up tumor assessment after Cycle 2) in Part 2 of the study may be replaced.

6.2.1.4 Subjects Lost to Follow-up

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

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

Should the subject continue to be unreachable, he/she will be considered withdrawn from the study.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7 STUDY INTERVENTIONS

7.1 Study Drug Administration

Subjects will receive dosing of HMPL-306 PO, QD, in each 28-day cycle.

Subjects should take HMPL-306 on an empty stomach (defined as no food ±2 hours of dosing) at a relatively fixed time every day, with about 240 mL of water. The accurate actual time of dosing should be recorded in the subject diary each time.

7.1.1 Part 1 (Dose Escalation)

In dose escalation, dosage will be according to dose level (see Table 5).

Dose escalation will begin at CCI mg QD of HMPL-306 in a 28-day continuous dosing treatment cycle. The dose will escalate successively according to the sequence of CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, CCI mg QD, and CCI mg QD.

7.1.2 Part 2 (Dose Expansion)

In dose expansion, HMPL-306 will be administered PO, QD, in a 28-day continuous dosing treatment cycle at MTD and/or RP2D.

7.2 Description of Products

HMPL-306 will be provided as a tablet formulation in 2 strengths: CCI mg and CCI mg.

7.2.1 Formulation, Storage, Preparation, and Handling

HMPL-306 is formulated as tablets, which are packaged in high-density polyethylene bottles, with 30 tablets per bottle. The contents of the label will be in accordance with all applicable regulatory requirements.

HMPL-306 should be sealed and stored in a secure, limited access area under appropriate conditions. The storage temperature should be between CCI °C to CCI °C with CCI [redacted]. HMPL-306 should not be used beyond the expiration date provided by the manufacturer.

The temperature-monitoring log should be recorded and filed in the study binder.

7.2.2 Drug Accountability

7.2.2.1 Assignment/Disposal (Study Site)

All study drug required for this study will be provided by the Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and that condition supplies will be replaced.

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

Study drug will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor or designee with appropriate

documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

7.2.2.2 Drug Return (Subject)

On Day -2 to Day 1, only drug assignment will be performed. The first dose of study drug should be administered on C1D1. Subjects will be provided with a pill diary and will be instructed on how to account for each day's dose appropriately. Subjects should return all unused study drug and containers from the previous cycle on Day 1 (date of scheduled visits) of each subsequent cycle, and the new study drug will be dispensed on the same day. Site study staff should review subject's pill diary and provide a new diary if necessary at the Day 1 visit of each cycle.

If a dose adjustment is required, the subject must return to the investigational site and return all unused study drug. The site must log into the eCRF, adjust the dose, reassign the drug serial number, and dispense new study drug dose to the subject. If the dose is adjusted a second time, the site must log into the eCRF and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PD during the previous cycle and the new drug has been dispensed, the subject must return all unused study drug on the 30-day safety visit after EOT.

7.3 Assessment and Verification of Compliance

The investigator is responsible for ensuring the subject's treatment compliance. The Sponsor will provide supervision through on-site monitoring visits made by its representatives. The investigators should maintain complete and accurate records of drug use. The dosing regimen and subject's actual dosing should be recorded in the original treatment records, as well as eCRF. At each treatment visit, the investigators or study staff should comprehensively assess the subject's treatment compliance according to the drug dispensing and return status at each visit and the actual dosing conditions, such as missed doses and overdosing reported by the subject. The subjects must return all drug bottles and remaining capsules at the end of the study. The investigational sites must return all remaining supplies and drugs to the Sponsor or provide evidence of destruction at the conclusion of the study.

7.4 Dose Adjustments

7.4.1 Adjustment of Dose within the DLT Assessment Window

In the DLT assessment window, subjects without DLT must not undergo dose reduction of HMPL-306.

- If a DLT occurs, HMPL-306 administration will be suspended and appropriate supportive treatment will be given
- If a DLT returns to Grade 1 or lower within 14 days, HMPL-306 may be resumed at the previous lower dose if the investigator assesses that the subject may still benefit
- If a DLT has not returned to Grade 1 (inclusive) or lower within 14 days, or DLT reoccurs at the lowered dose, HMPL-306 will be terminated

- If the subject has an AE that does not meet the DLT criteria, the subject should continue HMPL-306 according to the original planned dose; for Grades 3 and 4 non-DLT AEs, HMPL-306 can be suspended as necessary as assessed by the investigator

7.4.2 Dose Adjustment Outside the DLT Assessment Window (Including Dose Expansion Part)

Table 7 Dose Adjustment for Hematologic Toxicity

CTCAE v5.0 Grade	Action
Grade 1 or 2	None
Grade 3 or 4 (believed to be related to HMPL-306 and NOT underlying disease)	• Hold drug. • If the toxicity improves to Grade ≤2 within 28 days, then resume at original dose. • If the toxicity recurs at original dose, then resume at 1 dose lower provided the toxicity improves to Grade ≤2 within 28 days. • If the toxicity recurs in setting of prior dose level reduction, then resume at the next lower dose provided the toxicity improves to Grade ≤2 within 28 days. • In the event the toxicity does not improve to Grade ≤2 within 28 days or toxicity recurs despite 2 dose reductions, HMPL-306 treatment is to be permanently discontinued.

AE = adverse event; CTCAE v5.0 = Common Terminology Criteria of Adverse Events version 5.0.

Table 8 Dose Adjustment for Non-Hematologic Toxicity

CTCAE v5.0 Grade	Action
Grade 1 or 2	None
Grade 3[1]	• Hold drug. • If the toxicity improves to Grade ≤2 within 28 days then resume at original dose. • If the toxicity recurs at original dose, then resume at 1 dose lower provided the toxicity improves to Grade ≤2 within 28 days. • If the toxicity recurs in setting of prior dose level reduction, then resume at the next lower dose provided the toxicity improves to Grade ≤2 within 28 days. • In the event the toxicity does not improve to Grade ≤2 within 28 days or toxicity recurs despite 2 dose reductions, HMPL-306 treatment is to be permanently discontinued.
Grade 4[1]	• Permanently discontinue treatment with HMPL-306.

CTCAE v5.0 = Common Terminology Criteria of Adverse Events version 5.0.

1. Dose adjustments or modifications for Grade ≥3 nausea, vomiting, diarrhea, constipation, fatigue, and electrolyte imbalance are not required if they can be controlled by systemic or local drug administration.

7.4.3 Dose Adjustment for QT Interval Prolongation

Table 9 Dose Adjustment for QT Interval Prolongation

Degree of QTcF Prolongation	Action
QTcF >480 ms to 500 ms	• Hold drug. • Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medications with known QTcF interval-prolonging effects. Restart HMPL-306 at original dose if QTcF interval returns to ≤480 ms. • Monitor ECGs at least weekly for 2 weeks following resolution of QTcF prolongation.
QTcF >500 ms	• Hold drug. • Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTcF interval-prolonging effects. • Restart HMPL-306 at half of the original dose when QTcF interval returns to within 30 ms of baseline or ≤480 ms. • Monitor ECGs at least weekly for 2 weeks following resolution of QTcF prolongation. Consider re-escalating HMPL-306 to the original dose if an alternative etiology for QTcF prolongation can be identified.
QTcF interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue HMPL-306 permanently.

ECG = electrocardiogram; QT = interval from the start of the Q wave to the end of the T wave; QTcF = QT interval corrected for heart rate using Fridericia's formula.

7.4.4 General Dose Adjustment Note

The severity of DLTs/AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Reasons for dose modifications or delays, the supportive measures taken, and the outcome should be documented in the subject's chart and recorded in the eCRF.

- 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 subject has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of 1 grade and will be treated as Grade 1 toxicity for dose modification purposes

- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment can be continued at the same dose

- 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, treatment should be

discontinued. Continuation/resumption of treatment after an interruption of more than 14 days must be discussed with the medical monitor or his or her designee

- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed

7.5 Special Adverse Events Handling Principles

7.5.1 Handling Principles for Leukocytosis

Subjects who develop leukocytosis should be graded per NCI CTCAE Version 5.0 and treated by the following measures in a timely manner:

- Hydroxyurea oral therapy is immediately given, and it can be used at up to 2 to 3 g twice a day (see Table 10)
- Leukapheresis is performed if clinically necessary

When the above treatment measures are unable to effectively control the clinical symptoms, HMPL-306 treatment should be suspended. After the clinical symptoms have been fully relieved, the HMPL-306 administration can be resumed. The dose of the drug resumed should be decided after discussion with the Sponsor-appointed medical monitor.

Table 10 Hydroxyurea Initial Dose Reference

Hydroxyurea Dose	Peripheral White Blood Cell Count	Absolute Value of Increase from Baseline of Peripheral White Blood Cell Count
1000 mg QD	25×10^9/L to 50×10^9/L	15×10^9/L to $<30\times10^9$/L
2000 mg BID	$>50\times10^9$/L to 75×10^9/L	30×10^9/L to $<50\times10^9$/L
3000 mg BID	$>75\times10^9$/L	$\geq50\times10^9$/L

BID = twice daily; QD = once a day.

8 SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, whether or not considered related to the medicinal product.

8.1.2 Serious Adverse Event

An AE is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE. An event is considered "life threatening" if, in the view of the investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject 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
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

8.1.3 Dose-Limiting Toxicity

DLT is defined as the occurrence of any of the following TEAEs during the DLT assessment window, unless the TEAEs are clearly unrelated to the study drug or judged by the investigator as not clinically significant.

1. Non-hematologic toxicities:

- Any Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity, except for the following conditions:

– Recovered to Grade ≤1 within 3 days after supportive therapy is administered for nausea, vomiting, diarrhea, constipation, fatigue, and electrolyte imbalance
– Grade 3 hypothyroidism, adrenal gland or pituitary insufficiency, and inflammatory reactions at the tumor site

– Grade 3 hypertension downgraded to Grade ≤1 within 1 week with appropriate supportive therapy

2. Hematologic toxicity:

- Grade ≥3 febrile neutropenia (neutrophil count $<1.0\times10^9$/L, accompanied with a single body temperature measurement of ≥38.3°C or ≥38°C persisting for 1 hour)
- Grade 4 neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia accompanied with clinically significant bleeding, in addition to that requiring transfusion
- Grade 4 anemia requiring a dose delay of ≥14 days

3. Any life-threatening complication or abnormality not covered in the NCI CTCAE Version 5.0.

8.2 Adverse Event Reporting

8.2.1 Adverse Event Reporting Period

After signing of the pre-screening informed consent, AEs due to the protocol-required intervention will be collected in the pre-screening phase.

After signing of the main study informed consent, all SAEs and AEs regardless of attribution will be collected until 30 days after the last dose of study drug or start of a new treatment of antitumor therapy, whichever is earlier. The relevant AEs will be followed up until they are recovered to the baseline status, already in a stable state as assessed by the investigator, start of new antitumor therapy, loss to follow-up, death, withdrawal of informed consent, the end of study, or it has been confirmed that the AEs are unrelated to the study drug. After this period, the investigators should report only SAEs that are considered to be related to the study drug.

8.2.2 Expedited Reporting

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. 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. The following is a list of events that the investigator must report to the Sponsor within 24 hours after first learning of the event, regardless of relationship to study drug:

- SAEs
- Pregnancy

8.2.3 Dose Limiting Toxicity Reporting

For each DLT event that occurs in the dose escalation part, the investigator must confirm to the Sponsor within 2 business days after learning of it and should conduct phone or online meetings with the medical monitor and report any DLT events observed in the DLT evaluation window.

8.3 Prior and Concomitant Therapies

8.3.1 Prohibited Therapies

Any therapy intended for the treatment of cancer (with exceptions as noted in Section 8.3.2), whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Concomitant use of medications that have a known risk of causing QT prolongation and/or torsades de pointes (refer to Appendix 5).

HMPL-306 is a substrate of CCI [redacted]. The potential effects of medications that can affect the PK of HMPL-306 via CCI [redacted] pathway have not been tested in the clinic. During the study treatment period, medications that can CCI [redacted] (Appendix 6) should be avoided, and such drugs should be discontinued 1 week or 5 half-lives (whichever is longer) before the start of the study treatment.

Prophylactic use of antiemetic drugs or colony-stimulating factors, platelet irritation factor, or erythropoietin is not allowed during the DLT assessment window. Outside the DLT assessment window, it may be allowed if the investigator considers it necessary.

8.3.2 Permitted Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject. All concomitant therapy within 28 days prior to randomization and the Safety Follow-up visit should be reported to the investigator and recorded on the appropriate eCRF.

Subjects who use oral contraceptives, hormone-replacement therapy, or other allowed maintenance therapy may continue their use if indicated.

Prophylactic antiemetic, granulocyte colony-stimulating factors, granulocyte macrophage colony-stimulating factors, platelet-simulating factors, or erythropoietin are permitted as clinically indicated.

Levetiracetam is the preferred agent for epileptic prophylaxis. Other agents may be used but require prior discussion with the Sponsor before initiation unless medically urgent.

All supportive measures consistent with optimal subject care will be given throughout the study.

8.3.3 Drug-Drug Interactions

There are currently no data on a drug demonstrating clear interactions with HMPL-306 in the human body. In vitro data indicate that HMPL-306 exhibited an CCI [redacted]

CCI [redacted]

During the study treatment period, the use of medications that are CCI [redacted] (Appendix 7) should be avoided. If the investigator believes it is necessary to use it, consent of the Sponsor-appointed medical monitor should be obtained before use, and close observation should be performed during use for a possible reduction in efficacy or increase in toxicity due to drug interactions.

8.3.4 Rescue Therapies

Not applicable.

8.3.5 Duration of Follow-up for Adverse Events

The investigator will follow all unresolved AEs and SAEs until the events are resolved or stabilized, the subject is lost to follow-up, subject's death, or the end of the study. Resolution of AEs and SAEs (with dates) should be documented on the appropriate eCRF and in the subject's medical record to facilitate source data verification (SDV). For SAEs, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the eCRF.

For some SAEs, additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report) may be followed-up by telephone, fax, email, and/or a monitoring visit.

All pregnancies that occur during the study should be followed until pregnancy outcome.

8.4 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.5 Assessment of Severity

Investigators will seek information on AEs and SAEs at each subject contact. All AEs and SAEs, whether reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE/SAE form.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of severity through clinical description by referring to the 5-grade determination standard in the NCI CTCAE Version 5.0. Please use the guideline below for the assessment of severity when the observed or reported AE is not listed in the NCI CTCAE Version 5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs). (Note: Instrumental ADLs

refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs (Note: Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

8.6 Causality Assessment

Investigators should use their knowledge of the subject, the circumstances surrounding the AE, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug. To ensure consistency of causality assessments, investigators should apply the general guidelines as provided in Table 11 below:

Table 11 Determination of Correlation Between Adverse Events and Study Drug

Correlation	Criteria for Assessment
Not related	If there is no possibility of correlation between the event and the study drug, the adverse event will be deemed "unrelated" to the study drug. The situations that meet this assessment factor include, but are not limited to, the following: Adverse events caused by influence of underlying disease or concurrent disease or other drugs, unreasonable or no temporal relationship between the adverse events and the trial drug, and/or existence of other factors that may more likely lead to adverse events.
Related	If the event has a potential relationship with the study drug, the adverse event will be considered as "related" to the study drug. The situations that meet this assessment factor include, but are not limited to, the following: There is a reasonable temporal relationship between the adverse event and the study drug or the adverse event recurs after re-challenge; compared to the potential relationship with the study drug, the possibility of other factors that may cause the adverse event are not present, or the possibility is lesser or the same.

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.

8.7 Documenting Adverse Events

When an AE or SAE is recorded, the preferred medical terminology or concept should be used. Abbreviations and colloquialisms (eg, jargon or slang) should be avoided.

All AEs (including SAEs) should be recorded on the AE eCRF, and the check box for "Serious" should be ticked for entries that fit the criteria for SAEs. The investigator should also complete an SAE report and submit this to the Sponsor or its designee within 24 hours of knowledge of the event.

Only 1 medical concept should be recorded in the event field on the eCRF.

8.7.1 Diagnosis versus Symptoms and Signs

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, hepatic failure should be recorded instead of jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.7.2 Adverse Event Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause with the exception of severe or serious secondary events. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF if the dehydration is mild.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

8.7.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless the severity changes. If a persistent AE becomes more or less severe, it should be recorded again in a new eCRF entry. Please refer to the eCRF Completion Guidelines for information on completing each eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the eCRF.

8.7.4 Abnormal Laboratory Values or Abnormal Vital Signs

Not every laboratory abnormality/abnormal vital sign qualifies as an AE. A laboratory test result/abnormal vital sign must be reported as an AE if it is a change from baseline and meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

Investigators are responsible for reviewing all laboratory findings and abnormal vital signs and determining whether each abnormality should be reported as an AE.

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 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.

8.7.5 Preexisting Medical Condition

A preexisting medical condition is one that is present at Screening. Such conditions should be recorded on the eCRF as medical history. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study (excluding deterioration of the study disease conditions). When such events are recorded on the eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.7.6 Pregnancy

A female subject must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours of awareness to the Sponsor (the reporting period for pregnancy continues up to 30 days after completion of the study drug). The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until outcome of the pregnancy. Pregnancies occurring up to 30 days after the completion of the study drug must also be reported to the investigator.

Male subjects must also be instructed to inform the investigator immediately if their partner becomes pregnant during the study or within 100 days after the last dose of study drug. If such an event occurs, it should be reported as described above.

Pregnancy loss of any kind should always be classified as serious AE (as the Sponsor considers these medically significant), recorded on the eCRF, and expeditiously reported to Sponsor.

Any congenital anomaly/birth defect in a child born to a female subject or female partner of a male subject exposed to the study drug should be recorded and reported as an SAE.

8.7.7 Worsening of Malignancy

Worsening and/or progression of the subject's malignancy should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only. If there is any uncertainty about an AE being related only to the disease under study, it should be reported as an AE or SAE.

8.7.8 Death

All deaths that occur during the protocol-specified AE reporting period must have the underlying cause reported to the Sponsor as an SAE, with death listed as the outcome. Deaths due to the progression of disease must also be reported to the Sponsor as an SAE. Death events that occur after 30 days following the last dose of study drug must be reported to the Sponsor as an SAE only

if it is confirmed as related to study drug. If the primary cause of death is unknown and cannot be ascertained at the time of reporting, please record "Unknown cause death" on the eCRF, and the "unexplained/unknown death" should be reported expeditiously as an SAE. The SAE should be reported before the specific cause of death has been determined.

8.7.9 Overdose

For this study, any dose of HMPL-306 greater than the intended dose will be considered an overdose. No specific information is available on the treatment of overdose of HMPL-306. In the event of overdose, further HMPL-306 administration should be held, and the subject should be observed closely for signs of toxicities. Appropriate supportive treatment should also be provided if clinically indicated. In the event of accidental or intentional overdose, the investigator or other site personnel should inform the Sponsor study representatives immediately, or no later than 24 hours.

- An overdose with associated AEs/SAEs should be recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the case report form (CRF) and on the study drug CRF module
- An overdose with no associated signs or symptoms should only be reported on the study drug CRF module
- Overdose will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae

9 ANALYSIS

9.1 Statistics and Analysis Method

All statistical analyses 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), which will be finalized prior to the 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. No interim analysis is planned for the study. However, the accrued data from any cohort may be analyzed for internal decision-making purposes, for example, to provide information for a potential phase 3 study design.

9.1.1 Statistical Hypothesis

No formal hypothesis testing is planned for this study. For efficacy endpoints, the study will provide the estimates and the associated 95% CI for precision.

9.1.2 Sample Size Rationale

Approximately 122 to 131 subjects are estimated to be recruited based on the number of study cohorts and the number of study subjects included in each cohort. Subjects not evaluable for DLT will be replaced, and this may result in the number of subjects enrolled being more than expected.

9.1.2.1 Dose Escalation Part

The maximum sample size in this phase will be determined jointly by the Sponsor and the investigator. The exact sample size of the mTPI-2 design in the dose escalation part cannot be pre-specified because of the dynamic nature of the Bayesian allocation procedure. Subjects not evaluable for DLT will be replaced, and this may result in the number of subjects enrolled being more than expected. It is estimated that approximately 27 to 36 subjects may be enrolled at this part.

9.1.2.2 Dose Expansion Part

In order to better describe the safety of the recommended dose of single-dose HMPL-306 in future studies, approximately 95 subjects (4 cohorts of approximately 20 subjects and 1 cohort [C-1] of approximately 15 subjects) will be treated with HMPL-306 during this part. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 AE in 95 subjects is 100%, 99%, and 62%, respectively.

9.1.3 Analysis Sets

The following analysis sets are defined for the study:

- Safety analysis set: All enrolled subjects who received at least 1 dose of study treatment will be included in the safety analysis population. Safety evaluation will be performed based on the first dose of study treatment received by a subject. This is the primary population for the safety and efficacy analysis endpoint PFS.

- DLT evaluable analysis set: All subjects enrolled in the dose escalation phase of the study who are evaluable for DLT assessment. A subject is DLT evaluable if he/she meets the following criteria:
  - has received at least 75% of the assigned dose of study medication during the DLT assessment window

    OR
  - has not completed the DLT assessment period due to a DLT
- Response evaluable analysis set: All subjects who received study treatment and have a baseline tumor assessment and at least 1 postbaseline assessment will be considered evaluable for antitumor efficacy endpoints such as objective response rate (ORR), disease control rate (DCR), time to response (TTR), and duration of response (DoR)
- PK analysis set: All subjects with at least 1 quantifiable plasma concentration of HMPL-306 will be included in the PK analysis population
- PD analysis set: All subjects with at least 1 quantifiable level of 2-HG in the plasma will be included in the PD analysis population

9.2 Statistical Analysis

Data will be summarized by dose/disease cohorts. Continuous variables will be described using the observed number, mean, median, standard deviation, minimum, and maximum; categorical variables will be described using frequency. Kaplan-Meier method will be used to summarize the time-to-event data.

9.2.1 Subject Disposition

The number and percentage of subjects that were enrolled in the study, treated, and discontinued from study treatment will be presented for the Safety Analysis Set. The primary reason for treatment discontinuation will be summarized according to the categories in the eCRF. Subject disposition will be summarized overall and by tumor types.

Important protocol deviations will be summarized and listed by category.

9.2.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the Safety Analysis Set using descriptive statistics.

A summary of baseline subject and disease characteristics, diagnosis, medical history, prior therapies will be reported using descriptive statistics.

Other subject characteristics will be summarized as deemed appropriate.

9.2.3 Prior and Concomitant Medications

Prior medications will be defined as medications that stopped before the day of first dose of study treatment. Concomitant medications will be defined as medications that 1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or 2) started on or after the date of the first dose of study treatment 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. Prior and concomitant medication will be summarized overall and by tumor types. A listing of prior and concomitant medications will be provided.

9.2.4 Safety Analysis

The summary of exposure to the drug, AEs, AEs leading to drug modification or discontinuation including DLTs, changes in laboratory results, and changes in vital signs etc. will be presented. The severity of all AEs will be graded according to NCI CTCAE Version 5.0, and all AEs will be coded by Medical Dictionary for Drug Regulatory Activities (MedDRA).

Safety evaluation will include a summary of the following:

- Incidence of DLTs by grade (Dose Escalation part only)
- Incidence of TEAEs by grade
- Incidence of SAEs
- Incidence of Grades 3 and 4 abnormalities in safety-related laboratory parameters
- Incidence of TEAEs/TRAEs leading to HMPL-306 dose interruption, reduction, or treatment discontinuation

The number and frequency of subjects experiencing AEs will be summarized according to System Organ Class (SOC) and preferred term.

For drug exposure, the indicators including, but not limited to, the total exposure duration, cumulative dose, dose intensity, and relative dose intensity of HMPL-306 will be calculated.

For laboratory tests that can be graded based on NCI CTCAE Version 5.0, the corresponding changes in the test results will be summarized according to the grade. The changes in vital signs, ECG results, and ECOG PS scores from baseline will be summarized.

9.2.5 Pharmacokinetics Analysis

Evaluation on PK will be performed on the PK analysis set. Concentration data of HMPL-306 in plasma and glioma tissue samples will be tabulated and summarized using descriptive statistics (number of subjects [n], arithmetic mean with standard deviation, coefficient of variation [CV%], and geometric mean, median, minimum, and maximum), as appropriate. Plasma PK parameters will be tabulated and summarized by treatment using descriptive statistics (n, arithmetic mean with SD, CV%, geometric mean, median, minimum, and maximum), as appropriate.

The following plasma PK parameters of HMPL-306 will be determined:

- AUC_{0-t} area under the plasma concentration-time curve from time 0 to time of the last measurable concentration
- AUC_{tau} area under the concentration-time curve during 1 dosing interval
- C_{max} maximum observed plasma concentration
- T_{max} time to reach the maximum plasma concentration

- C_{min} minimum observed plasma concentration
- C_{trough} observed plasma concentration at the end of a dosing interval (taken directly before the next dose administration)
- CL/F total plasma clearance of drug after extravascular administration, uncorrected for absolute bioavailability, calculated as dose/$AUC_{0-\tau}$ after multiple dose
- AR accumulation ratio

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.

Additional PK parameters may be included if deemed appropriate. Details of the PK analysis, including data handling rules and software used to perform the PK analysis, will be provided in the SAP.

9.2.6 Pharmacodynamic Analysis

Levels of 2-HG in the plasma and in glioma tissue samples will be tabulated and summarized using descriptive statistics (n, arithmetic mean with SD, CV%, geometric mean, median, minimum, and maximum), as appropriate. The correlation between the exposure level of HMPL-306 and 2-HG level and percent inhibition will be analyzed using descriptive and graphical means. Details of 2-HG analysis will be provided in the SAP.

9.2.7 Efficacy Analysis

The investigator shall evaluate efficacy according to the corresponding criteria for all subjects according to RECIST Version 1.1 (RANO criteria for glioma subjects).

Efficacy evaluation indicators include ORR, DCR, DoR, TTR, PFS, and OS.

- ORR: Defined as the proportion of subjects achieving a best overall response of confirmed complete response (CR) or partial response (PR)
- DCR: Defined as the proportion of subjects achieving a best overall response of confirmed CR, PR, or stable disease (SD)
- DoR: Defined as the time from the first occurrence of PR or CR, whichever comes first until disease progression or death
- TTR: Defined as the time from the start of study treatment to the first occurrence of objective response (PR or CR, whichever comes first)
- PFS: Defined as the time (months) from the start of study treatment until the first radiographic documentation of objective progression as assessed by the investigator using RECIST Version 1.1 or death from any cause
- OS: Defined as the time from the start of the study drug until death from any cause

The estimate of ORR and DCR and the corresponding 95% CI will be presented by tumor type. For time-to-event endpoints such as PFS, TTR, DoR, and OS, the medians and rates at various time points along with 95% CI will be estimated by Kaplan-Meier methodology.

9.2.8 Exploratory/Biomarker Analysis

This study will conduct detection and analysis on related biomarkers and will explore the biomarker predicting PK/PD correlation and antitumor effects. Exploratory biomarker evaluations may not be included in the clinical study report (CSR), and a separate summary report will be prepared.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, consensus, and the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, Applicable ICH Good Clinical Practice (GCP) Guidelines that have their origin in the Declaration of Helsinki, and applicable regulations and guidelines governing clinical study conduct.

10.2 Ethics Review

The Independent Ethics Committee (IEC)/Institutional Review Board (IRB) must review the protocol and amendments, IB, informed consent form (ICF), study-relevant materials (such as advertisements for subject recruitment), and any other essential documents. IEC/IRB approval is to be obtained prior to the start of the study at the investigator site.

All amendments are to be reviewed and approved by the IEC/IRB and applicable regulatory authorities (as required) and documented. All SAEs and 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 subject'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 IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, 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 Informed Consent

- Investigators or designees must obtain the signed ICF from subjects 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 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center
- Subjects must be informed that they may withdraw consent to participate in the study without any limitations. If the subject cannot sign the ICF, a legally acceptable representative of the subject must sign the ICF
- If the subject 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 subject and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the subject 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 risk/benefit assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to subjects (including subjects who have already received the study drug)

10.4 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 subjects by not disclosing subject-related information to third parties without authorization. eCRFs and other documents submitted to the Sponsor should not contain the subject's name.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- Subjects are identified only by the unique identifier. Investigators may retain the identification forms, which include subject numbers, names, and addresses. ICFs and other documents should be documented properly and should not be given to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Disclosure

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

10.6 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 subject medical records in the subject files as original source documents for the study.
- All participant data relating to the study will be recorded on 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, electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC 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]).

10.7 Biological Specimens and Data

For participants who provide informed consent agreeing to participate in future biomedical research, any unused samples for study-related research, as well as unused PK samples, may be stored for no longer than 15 years, or other period as per local requirements, after the final date of the database lock. After this storage period, any residual samples will be destroyed. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. The unused samples may be utilized for future biomedical research as permitted by local regulations. The results of these future biomedical research analyses will not be shared with subjects and will not be presented in the CSR.

If there are specific site or country requirements involving the pharmacogenomic analyses that the Sponsor is unable to comply with, samples will not be collected at those sites.

All samples will be single/double coded as defined by ICH guideline E15.

11 OVERSIGHT

11.1 Independent Monitoring

No independent data monitoring is planned for this study. The Sponsor will review study safety data on an annual basis, or more frequently, if safety concerns arise.

11.1.1 Safety Review Committee

- Participant safety will be continuously monitored by the SRC, which includes safety signal detection at any time during the study
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to HMPL-306 administration. An initial safety review for this study is planned for the first 3 participants who are dosed and have provided safety data for 28 days after administration of dose specified in Table 5, depending on the assigned cohort
- All safety data collected will be summarized and reviewed by the SRC for agreement of next steps
- In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to re-evaluate the study
  - Any deaths, regardless of causality
  - In addition, safety data will be reviewed on an ongoing basis during study conduct. At a minimum of twice a year, study data will be summarized and reviewed with investigators to identify potential safety signals. Additional safety review meetings may be scheduled based on concerns of the Sponsor or investigators
- Enrollment will be paused during the review. If a stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.

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 the 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 subject records, the accuracy of entries on the eCRFs, the adherence to 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 field 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 IRB/IEC representative may visit the site to perform audits or inspections, including SDV. 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 subject to audit or inspection include, but are not limited to, all source documents, eCRFs, medical records, correspondence, ICFs, IRB/IEC 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 subject 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 subjects, including screen failures, data will be collected on source documents first. The principal investigator (PI) is responsible for assuring that the data entered into eCRFs are complete and accurate and that entry and updates are performed in a timely manner. Data from ECG 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 the final responsibility for the accuracy and authenticity of all clinical and laboratory data entered into the EDC. Subject source documents are the investigator's/physician's subject 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 subjects that support the information entered into 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 subject'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 the 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 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 subject 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 subjects required for the study is enrolled earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, 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 subject and should assure appropriate subject 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 PK, PD, AND BIOMARKER ASSESSMENTS (EXCLUDING COHORT C-1)

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Samples for PK	Blood Samples for 2-HG	Blood Samples for Gene Mutation Analysis	ECG
Screening				X	X[2]	X
C1D1	Predose[1]		X	X		X[4]
	0 h	X				
	0.5 h (± 2 min)		X			
	1 h (± 5 min)		X			X[4]
	2 h (± 10 min)		X			X[4]
	3 h (± 10 min)		X			
	4 h (± 15 min)		X			X[4]
	6 h (± 15 min)		X			
	8 h (± 15 min)		X			
C1D2	Predose[1]		X	X		
	0h	X				
C1D8	Predose[1]		X	X		
	0 h	X				
C1D15	Predose[1]		X	X		
	0 h	X				
C1D22	Predose[1]		X	X		
	0 h	X				
C2D1	Predose[1]		X	X	X[3]	X[4]
	0 h	X				
	0.5 h (± 2 min)		X			
	1 h (± 5 min)		X			X[4]
	2 h (± 10 min)		X			X[4]
	3 h (± 10 min)		X			
	4 h (± 15 min)		X			X[4]
	6 h (± 15 min)		X			
	8 h (± 15 min)		X			
C2D2	Predose[1]		X			
	0 h	X				
C2D15	Predose[1]		X	X		
	0 h	X				
C3D1	Predose[1]		X	X	X[3]	X
	0 h	X				
C5D1	Predose[1]		X	X	X[3]	X
	0 h	X				

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Samples for PK	Blood Samples for 2-HG	Blood Samples for Gene Mutation Analysis	ECG
C7D1	Predose[1]		X	X	X[3]	X
	0 h	X				
C10D1 and every 3 cycles thereafter	Predose[1]		X	X	X[3]	X
	0 h	X				
EOT (Within 7 days after the last dose)	Anytime			X	X[3]	
Safety Follow-up period (30 days after EOT Visit)	Anytime					X

2-HG = 2-hydroxyglutaric acid; CxDx = Cycle X Day X; ECG = electrocardiogram; EOT = end of treatment; PD = pharmacodynamics; PK = pharmacokinetics.

1 Should be performed within 30 minutes before the dosing on that day and approximately 24 hours (±60 minutes) after dosing on the previous day (ie, Day 1 of Cycle 1 or 2).

2 Whole blood will be collected for potential analysis of CCI [redacted] at baseline in dose escalation and dose expansion. Samples collected in dose expansion will also be used for analysis of gene mutation abundance.

3 Whole blood will be collected in dose expansion only for analysis of gene mutation abundance, such as *IDH1*, *IDH2* (R140 and R172), CCI [redacted], etc.

4 To be performed in triplicate with intervals of approximately 5 minutes.

APPENDIX 2 PK, PD, AND BIOMARKER ASSESSMENTS FOR COHORT C-1

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Samples for PK	Blood Samples for 2-HG	Blood Samples for Gene Mutation Analysis	Glioma Samples for 2-HG and PK	ECG
Screening				X	X[2]		X
D1	Predose[1]		X	X			X[3]
	0 h	X					
	0.5 h (±2 min)		X				
	1 h (±5 min)		X				X[3]
	2 h (± 10 min)		X				X[3]
	3 h (± 10 min)		X				
	4 h (± 15 min)		X				X[3]
	6 h (± 15 min)		X				
	8 h (± 15 min)		X				
D2	Predose[1]		X	X			
	0h	X					
D8	Predose[1]		X	X			
	0 h	X					
D15	Predose[1]		X	X			
	0 h	X					
D22	Predose[1]		X	X			
	0 h	X					
D28	Predose[1]		X	X	X[2]		X[3]
	0 h	X					
	0.5 h (± 2 min)		X				
	1 h (± 5 min)		X				X[3]
	2 h (± 10 min)		X				X[3]
	3 h (± 10 min)		X				
	4 h (± 15 min)		X				X[3]
	6 h (± 15 min)		X				
	8 h (± 15 min)		X				
D29	24 h (± 30 min)		X				
Surgery	Anytime		X	X		X	
C1D1	Predose[1]		X	X			
	0 h	X					
C1D15	Predose[1]		X	X			
	0 h	X					
C2D1	Predose[1]		X	X			X
	0 h	X					

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Samples for PK	Blood Samples for 2-HG	Blood Samples for Gene Mutation Analysis	Glioma Samples for 2-HG and PK	ECG
C2D15	Predose[1]		X	X			
	0 h	X					
C3D1	Predose[1]		X	X	X[2]		X
	0 h	X					
C5D1	Predose[1]		X	X	X[2]		X
	0 h	X					
C7D1	Predose[1]		X	X	X[2]		X
	0 h	X					
C10D1 and every 3 cycles thereafter	Predose[1]		X	X	X[2]		X
	0 h	X					
EOT (within 7 days after last dose)	Anytime			X	X[2]		
Safety Follow-up period (30 days after termination of treatment)	Anytime						X

2-HG = 2-hydroxyglutaric acid; CxDx = Cycle X Day X; ECG = electrocardiogram; EOT = end of treatment; PD = pharmacodynamics; PK = pharmacokinetics.

[1] Should be performed within 30 minutes before the dosing on that day and approximately 24 hours (±60 minutes) after dosing on the previous day (ie, Day 1 of Cycle 1 or 2).

[2] Whole blood will be collected for analysis of gene mutation abundance, such as *IDH1*, *IDH2* (R140 and R172), CCI [redacted], etc. Samples collected at screening will also be used for potential analysis of CCI [redacted].

[3] To be performed in triplicate with intervals of approximately 5 minutes.

APPENDIX 3 ECOG PERFORMANCE STATUS

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

ECOG = Eastern Cooperative Oncology Group.

APPENDIX 4 PROHIBITED MEDICATIONS

Medications that can prolong QT interval are listed in Table 12 below:

Table 12 Medications That Can Prolong QT Interval

Aclarubicin	Ibogaine
Amiodarone	Ibutilide
Anagrelide	Levofloxacin
Arsenic trioxide	Levomepromazine
Azithromycin	Levosulpiride
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Cilostazol	Ondansetron
Ciprofloxacin	Oxaliplatin
Citalopram	Papaverine hydrochloride
Clarithromycin	Pentamidine
Cocaine	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Donepezil	Roxithromycin
Dronedarone	Sevoflurane
Droperidol	Sotalol
Erythromycin	Sulpiride
Escitalopram	Sultopride
Flecainide	Terlipressin
Fluconazole	Terodiline
Halofantrine	Thioridazine
Haloperidol	Vandetanib

This is not an exhaustive list of drugs that can prolong QT intervals, with the list of the latest drugs that can be found in the following link: https://crediblemeds.org/healthcare-providers/

APPENDIX 5 NEW YORK HEART ASSOCIATION FUNCTION CLASSIFICATION

Grading	Description
Level I	There is no restriction on physical activity: Daily physical activities do not cause asthenia, palpitations, dyspnea, or angina.
Level II	Mild limitation of physical activity: Feel good during rest, but daily physical activities can cause asthenia, palpitations, dyspnea, or angina.
Level III	Significantly limited physical activity: There is no subjective symptom when resting, but activities that are less than daily physical activities can cause the above symptoms.
Level IV	Unable to engage in any physical activities without discomfort: Symptoms occur even when resting. There will be increased discomfort when performing any physical activities.

Source: New York Heart Association. Naming and Diagnostic Criteria for Cardiovascular Disease, Version 9. Boston, MA: Little, Brown & Co; 1994: pp. 253-6.

APPENDIX 6 CCI [redacted]

CCI [redacted]

CCI [redacted]

Source: https://www.drugbank.ca

Note: This is not an exhaustive list containing all CCI [redacted]. The investigator should carefully consider the concomitant medication of each subject, assess the risk-benefit ratio, and perform appropriate monitoring.

APPENDIX 7 LIST OF CCI [redacted]

CCI [redacted]

CCI [redacted].

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1

Note: This is not a detailed list containing all CCI [redacted]. The investigator should carefully consider the concomitant medication of each subject, assess the risk-benefit ratio, and perform appropriate monitoring.

APPENDIX 8 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST VERSION 1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors (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 nonmeasurable as described below.

1.1.1 Measurable Tumor Lesions

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

- 10 mm by CT or magnetic resonance imaging (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 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 is preferred over chest X-ray, particularly when progression is an important endpoint, since CT 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 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 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 intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT 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 is done, the decision as to whether non-contrast CT 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 one measurable lesion, as detailed above.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two 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 one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two 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 two dimensions in the plane in which the image is obtained (for CT 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 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 one 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 zero even if complete response 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 trials 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 (eg, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial 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 that 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 (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, 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, 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 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 13 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 14 is to be used.

Table 13 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 14 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 trials; 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 not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually, the case is also considered not evaluable 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 Not Evaluable (NE), unless the sum of the diameters of the remaining target lesions which were assessed is greater than 20% from nadir, in which case target lesion response should be PD. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be NE, except where there is clear progression for the remaining non-target lesions which were assessed. Overall response would be NE if either the target response or the non-target response is NE except where this is clear evidence of progression.

2.4.3 Best Overall Response: All Time points

The best overall response is determined once all the data for the patient are known. Best response determination in trials where confirmation of CR or PR **is not** required: Best response in these trials is defined as the best response across all time points (eg, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the 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 and PD at second assessment 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 not evaluable.

Best response determination in trials where confirmation of CR or PR **is** required: CRs or PRs 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 best overall response can be interpreted as in Table 15.

Table 15 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

Table 15 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
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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the 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 the minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest that 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 a "normal" size (<0 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 an 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 13 and Table 14.

For equivocal findings of progression (eg, very small and uncertain new lesions and 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 nontarget lesion.

2.5 Frequency of Tumor Re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and should be 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, a 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 nontarget 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 the 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 the "time to an event" (eg, time to progression, disease-free survival, and progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol-specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (eg, 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 trials where response is the primary endpoint, confirmation of PR and CR is required to ensure that 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 trials. However, in all other circumstances, for example, in randomized trials (phase 2 or 3) or in studies where SD or PD are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, particularly 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 CR 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 trials, 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 trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD, as well as the progression-free survival, is 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 parts, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 9 RESPONSE ASSESSMENT IN NEURO-ONCOLOGY CRITERIA FOR GLIOMAS

Patients should be assessed with the same imaging method throughout the trial, with pre-specified imaging parameters.

General minimum imaging protocol of low-grade glioma:

Basic Magnetic Resonance Imaging Protocol (All Centers)

- Axial fluid-attenuated inversion recovery (FLAIR) (canthomeatal alignment): 3- to 5-mm sections, 1-mm interslice gaps, slice registration preserved as much as possible between sequential studies
- Axial T2: 5-mm sections, 1-mm interslice gap
- Coronal T1: 5-mm sections, 1-mm interslice gap
- Post-gadolinium chelate (contrast agent as per local clinical practice): coronal T1 and axial T1

(Alternatively, pre-gadolinium and post-gadolinium volumetric T1 may replace axial and coronal T1-weighted sequences)

Response	Criteria
Complete response	Complete response requires all the following criteria compared with the baseline scan: • complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely) • no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • patients must be off corticosteroids or only on physiological replacement doses • patients should be stable or improved clinically.
Partial response	Partial response requires all of the following criteria compared with the baseline scan: • greater than or equal to 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline • no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
Minor response	Minor response requires the following criteria compared with baseline: • a decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared with baseline • no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
Stable disease	Stable disease is present if the changes do not qualify for complete, partial, or minor response or progression and requires: • stable area of non-enhancing abnormalities on T2 or FLAIR imaging • no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement

Response	Criteria
	• patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
Progressive disease (≥12 weeks after radiation therapy completion)	Progression is defined by any of the following: • development of new lesions or increase of enhancement (radiological evidence of malignant transformation) • a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events • definite clinical deterioration not attributable to other causes apart from the tumour, or decrease in corticosteroid dose • failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.

FLAIR = fluid-attenuated inversion recovery; MR = magnetic resonance.
Source: Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diff use low-grade gliomas. Lancet Oncol. 2011;12:583-93 [van den Bent et al 2011].

APPENDIX 10 COVID-19 RISK ASSESSMENT

HUTCHMED Limited acknowledges that the participants to be enrolled in this study are patients with refractory cancer, and therefore, may be at higher risk for complications if they contract COVID-19. Available data indicate that the elderly and people with underlying health conditions such as chronic respiratory, cardio-vascular or kidney disease, diabetes, active cancer, and more generally severe chronic diseases are more vulnerable to experience complications. However, there is an unmet medical need for new medications that are safe and effective in patients with refractory cancer who have limited treatment options.

During the COVID-19 pandemic, additional risks to subjects may exist either related to going to a healthcare facility (eg, being outside of home, possible contact with unsanitized surfaces) or as a result of study-related activities (eg, interaction with study staff). Potential subjects with known or suspected COVID-19 infection are ineligible. Subjects with a known COVID-19 infection may be considered for participation following 2 subsequent negative tests are provided. Patients may be screened and enrolled if the site has procedures in place to test and appropriately follow new patients on trial and to ensure patient safety and data integrity. It is at the Principal Investigator's discretion to balance the risk/benefit, and patient safety should always be considered.

Risk management steps being taken by HUTCHMED Limited and its designee:

4. Subject safety

    - Subjects will be educated by the investigator on COVID-19-related risks (ie, using cancer patient guidelines at ESMO web site).
    - Minimize time subjects spends at the clinic
        - Blood sampling/visit may be performed at another location (if this can be done within local restrictions on social distancing) to reduce site burden and risk for infection, eg, local laboratory, home nurse, or opening a satellite site. The laboratory results must be reviewed by the investigator, the local laboratory included on the 1572, and laboratory normal ranges must be collected.
        - Study visits may be conducted with subjects using telemedicine, where the investigator and site can videoconference with the patient. In this setting, investigators should perform as many assessments as possible, including any AEs, concomitant medications, and ECOG performance status.
    - Reduce the risk for COVID-19 infection while travelling to and from the clinic by providing an option, where allowed, for car/taxi service to avoid public transportation.
    - If a subject enrolled into the study subsequently tests positive for COVID-19, the data will be entered into the eCRF as an AE with proper source documentation.

5. Investigational Medicinal Product handling

    - Investigational Product may be delivered to the subject's house if permitted under the site's Standard Operating Procedures and patient chain of custody and patient privacy is protected.

6. Management of protocol deviations due to the COVID-19 pandemic

   HUTCHMED Limited and its designee will adhere to all applicable health authority guidelines for documenting and reporting any protocol deviations due to the COVID-19 pandemic. The deviations will be reported as instructed to the authorities or institutional review boards/independent ethics committees.

7. Remote monitoring

   HUTCHMED Limited and its designee agree to perform remote monitoring where feasible and permitted. For remote source data verification, country legislation will be followed and performed only where allowed with written agreement of the Principal Investigator. The planned site-level procedures will be described in detail and approvals sought as required. If a site cannot support remote monitoring with electronic medical records (EMR) access, the site will not be permitted to consent new patients. Remote visits will also be conducted to facilitate site selection and training.

The risk-benefit ratio for subjects enrolled according to the inclusion and exclusion criteria defined in the study protocol and according to the defined COVID-19 risk mitigation measures continues to be favorable.

HUTCHMED Limited and its designee will continue to evaluate the impact of COVID-19 on the ability of each site to initiate and execute the trial. Site-specific positions will be evaluated prior to the Site Initiation Visit, with the outcomes and any resultant actions documented and filed in the Trial Master File.

As the COVID-19 situation may be temporary, regulatory guidance will be continuously re-evaluated and any changes will be communicated as necessary.

APPENDIX 11 RATIONALE FOR STUDY POPULATION SELECTION

Cohort A: Cholangiocarcinoma

This study plans to enroll subjects with locally advanced or metastatic cholangiocarcinoma not eligible for curative resection or transplantation, who previously received ≥1 gemcitabine- or 5-fluorouracil-containing regimen.

The current European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Biliary Cancer indicates that the first line setting for locally advanced or metastatic disease is a gemcitabine-based combination, or gemcitabine monotherapy based on the patient's performance status. However, there is no standard second-line chemotherapy, or targeted therapy indicated; and there is no established second-line systemic therapy following progression after first-line treatment (Valle 2016).

Additionally, a Phase 3 study of AG-120 (IDH1 inhibitor) in patients with cholangiocarcinoma harboring mutant IDH1 (mIDH1) conducted in the United States (US) and European Union (EU) (NCT02989857), supports the use of an IDH inhibitor in the proposed setting. This study enrolled patients with documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease and must have received at least 1 gemcitabine- or 5-fluorouracil (FU) containing regimen. Patients in this study achieved a statistically significant improvement in median progression-free survival (PFS) over placebo (2.7 months versus 1.4 months; hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.25-0.54; p<0.0001). Treatment with AG-120 was well tolerated, and no treatment-related deaths occurred (Abou-Alfa 2020).

Cohort B: Chondrosarcoma

This study plans to enroll subjects with locally advanced or metastatic skeletal chondrosarcoma.

The current ESMO Clinical Practice Guidelines for bone sarcomas indicate that primary bone tumors are rare, and account for <0.2% of malignant neoplasms registered in the EUROCARE database. Given the rarity of the disease and the complexity of management, the accepted standard for bone sarcomas is treatment at reference centers and/or within reference networks able to provide access to the full spectrum of care and age-specific expertise. In these centers/networks, therapy is either clinical studies or locally established treatment protocols. Standard treatment practices can vary from center-to-center, and can further vary based on the disease subtype, and patient characteristics (Casali 2018).

Despite the lack of clear treatment options for these patients, there is emerging data for IDH inhibitors for the treatment of patients with chondrosarcomas harboring IDH mutations. An ongoing Phase 1 study of AG-120 (IDH1 inhibitor) enrolled 21 patients with locally advanced or metastatic chondrosarcoma harboring mIDH1. Among the 21 patients enrolled, 11 patients (52.4%) received prior systemic therapy. Patients achieved a median PFS of 5.6 months (95% CI, 1.9 to 7.4 months); the PFS rate at 6 months was 39.5%, and 11 patients (52.4%) experienced stable disease. AG 120 also showed minimal toxicity and durable disease control (Tap 2020).

Cohort C: Glioma

This study plans to enroll subjects with recurrent Grade 2 gliomas that are not a candidate for clinical resection.

Isocitrate dehydrogenase mutations are highly prevalent in patients with low-grade glioma, occurring in up to approximately 80% of all cases. However, given the toxicities associated with

chemotherapy and radiation, there remains a significant unmet need to improve treatment options for patients living with IDH mutant gliomas. Standard treatment consists of resection, followed by radiation and chemotherapy. Treatment is not curative and current therapy is associated with short- and long-term toxicity. Upon recurrence, due to heterogeneity of disease, there is no one standard treatment regimen. Both EU and US guidelines recommend repeat surgery, alkylating chemotherapy re-irradiation, or experimental therapy (Weller 2021; NCCN 2020).

In accordance with the treatment guidelines, a recent study of AG-881, a dual IDH1/2 inhibitor, enrolled patients with gliomas (enhancing or non-enhancing disease) who have recurred or progressed following standard therapy OR have previously untreated disease (NCT02481154). This study enrolled 22 non-enhancing glioma patients, who had a median of 2 prior lines of treatment (range: 1-4). An objective response rate (ORR) of 13.6% was achieved, and 77.3% of patients achieved stable disease. At 24 months, 60.5% of patients were still alive, and progression free (Mellinghoff 2020). These study results showed encouraging preliminary activity with prolonged disease control, and reduced growth of non-enhancing tumors that warrants further exploration of IDH1/2 inhibitors in an underserved patient population.

Cohort D: Other Solid Tumors with an IDH1/2 Mutation

This study plans to enroll subjects with any other locally advanced or metastatic solid tumor harboring an IDH mutation that has progressed on at least 1 line of prior therapy.

Therapies for patients with locally advanced or metastatic solid tumors are palliative and not curative. Therefore, there is an unmet medical need for additional therapies. While IDH1/2 mutations are most commonly observed in diseases covered by cohorts A to C of the proposed clinical study, these mutations are also found less commonly in other solid tumors. In the absence of approved therapies targeting IDH mutations, solid tumors harboring IDH mutations are treated with standard of care agents according to anatomical site, such as cytotoxic chemotherapy that is not tailored to the characteristics of individual patient's tumor. As a result, patients receive therapies that may not be of benefit, while exposed to potential toxicities. Cohort D will provide an additional treatment option for patients who have incurable malignancies. The requirement of at least one prior therapy should ensure patients do not forego significantly effective palliative therapy in lieu of the proposed investigational agent (HMPL-306), but rather have an opportunity to explore a new potential treatment tailored to their tumor characteristic. Furthermore, there is no limit to the number of prior therapies (with the exception of IDH1/2 inhibitors) for a patient to qualify. Lastly, study participants may receive additional approved therapies should they exist after participation on the proposed clinical study.

APPENDIX 12 AMENDMENT HISTORY

Amendment 1 (29 October 2020) Summary

Section Number	Summary of Change	Rationale for Change
Section 4.1.1 - Part 1 (Dose Escalation) Table 6 mTPI-2 Decision Table for Dose Selection	• Revised DLT rate to 25% and subsequent changes to DLT/cohort parameters • Specified minimum of 3 patients per cohort at each dose level • Updated mTPI-2 table to reflect DLT rate of 25%	Request by FDA
Section 7.4.3 - Dose Adjustment for QT Interval Prolongation	Deleted provision for allowing intra-subject dose escalation	Request by FDA
Section 8.1.3 - Dose-Limiting Toxicity	Revised DLTs to: • Exclude non-hematologic AEs that recover to Grade ≤1 or lower within 3 days after supportive therapy is administered for nausea, vomiting, diarrhea, constipation, fatigue, and electrolyte imbalance • Include any Grade 4 neutropenia • Include Grade 3 thrombocytopenia accompanied with clinically significant bleeding, in addition to that requiring transfusion.	Request by FDA
Section 6.1.9 - Ophthalmologic Assessments Section 1.3 - Schedule of Events	• Revised ophthalmologic assessments to include optical coherence tomography as part of the routing ocular monitoring • Revised ophthalmologic assessments to include an OCT assessment at 6 weeks	Request by FDA
Section 5.2 - Inclusion Criteria	• Revised inclusion criterion #9 to only allow patients to be eligible after all toxicities are recovered to at least Grade 1 from any prior therapy • Revised inclusion criterion #14 to specify tumor tissue samples must be used for IDH mutation determination	Request by FDA

	• Revised inclusion criterion #16 to specify that only validated NGS of tumor tissue is permitted for documentation of IDH mutation for Part 2 eligibility	
Section 7.4.2 - Dose Adjustment Outside the DLT Assessment Window (Including Dose Expansion Part)	• Added Table 7 - Dose Adjustment for Hematologic Toxicity • Added Table 8 - Dose Adjustment for Non-hematologic Toxicity	Request by FDA
Table 3 Summary of Potential Risks of HMPL-306	Added potential Risk of QTc interval prolongation	Request by FDA
Section 6.1.10.10 - IDH Mutational Status	Added in collection of information on IDH mutational test methodology for patients in Part 1.	Request by FDA
Section 7.4.3 - Dose Adjustment for QT Interval Prolongation	Added Table 9 - Dose Adjustment for QT Interval Prolongation	Request by FDA
Table 5 Subject Dose Grouping (Dose Escalation Plan)	Deleted specification that subjects in dose escalation will receive 1 single dose of HMPL-306, 7 days prior to C1D1	Correct an error
Section 5.3 - Exclusion Criteria #10	Lowered the exclusion criteria heart rate-corrected QT (QTc) interval from >480 ms to ≥470 ms	Recommendation by FDA

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