STATISTICAL ANALYSIS PLAN

A Multicenter, Open-Label Phase 1 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
Name of Test Drug:	HMPL-306
Phase:	Phase 1
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Compliance: The study described in this report was performed according to the principle of Good Clinical Practice (GCP).

APPROVAL SIGNATURES

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REVISION HISTORY

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ATC	anatomic therapeutic classification
BMI	body mass index
BOR	best overall response
CFB	change from baseline
CI	confidence interval
COVID	coronavirus disease 2019
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
GCP	Good Clinical Practice
HG	hydroxyglutaric acid
ICF	inform consent form
ICH	International Council on Harmonization
IDH	isocitrate dehydrogenase
IV	intravenous(ly)
LLQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MUGA	multiple-gated acquisition
NCA	non-compartmental analysis
NCI	National Cancer Institute
MTD	maximum tolerated dose
NET	neuroendocrine tumor
ORR	objective response rate

Abbreviation	Term
OS	Overall survival
PD	progressive disease
PD-L1	programmed death-Ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PO	oral(ly)
PR	partial response
PT	preferred term
QD	once daily
QTcF	QT interval corrected by the method of Fredericia
RANO	Response Assessment in Neuro-Oncology
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
TLF	table, listing, figure
TPR	timepoint response
TTR	time to response
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study 2020-306-GLOB2. The SAP is based on the Protocol Version Amendment 3, dated 06 December 2022.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

Though there is no protocol amendment, it was noted that the study did not proceed to the dose expansion part. That is, no patients were enrolled to the expansion cohorts A (cholangiocarcinoma), B (skeletal chondrosarcoma), C (low-grade glioma), C-1 (perioperative glioma), and D (any other solid tumor harboring an IDH mutation). Hence, the analysis of the study will be conducted only for the dose escalation part. And this analysis plan is only for the part 1, dose escalation part. For the information of part 2, expansion part, please refer to this study protocol.

The analysis related to exploratory PK endpoints will be described in a separate analysis plan.

2. STUDY DETAILS

2.1. Study Objectives

The objectives and corresponding endpoints are summarized in Table 1.

Table 1 Objectives and Corresponding Endpoints of Part 1- Dose Escalation

Tier	Objectives	Endpoints
Primary	To evaluate the safety and tolerability of HMPL-306, thereby determining the RP2D and/or the MTD of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutations	MTD and/or RP2D Safety including DLTs, TEAEs, SAEs, ECGs, and clinical laboratory abnormalities
Secondary	To assess the preliminary antitumor activity of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutations	ORR, DCR, DoR, TTR, and PFS
	To assess the PK of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutation	Observed plasma concentrations and PK parameters of HMPL-306
	To assess the PD of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutation	Observed plasma concentrations of 2-HG
Exploratory	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
	To explore the influence of gene abnormalities other than IDH mutations on safety, efficacy, PD, and PK	
	To assess the potential predictive biomarkers or response or progression though collection of serial ctDNA collection	

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.

2.2. Study Design

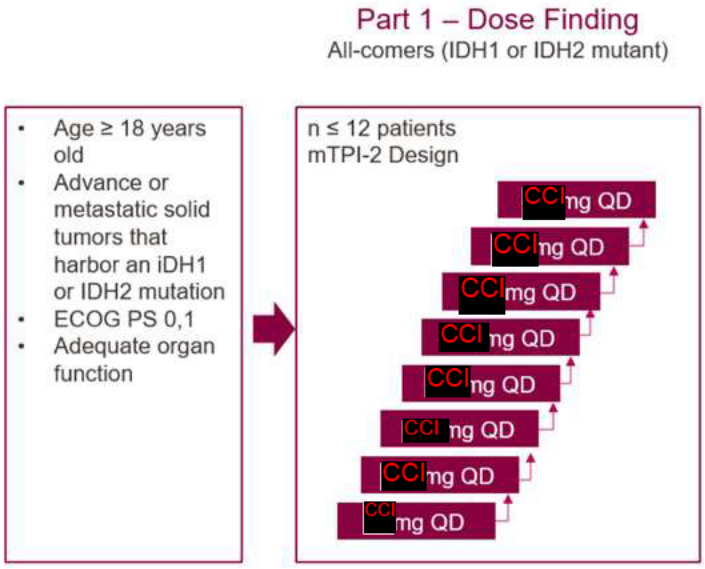
This is a phase 1, open-label, multicenter study to evaluate the safety and tolerability of HMPL 306 administered orally (PO) in treatment of patients with locally advanced or metastatic solid tumors with IDH mutation. The study consists of 2 parts: Part 1 (dose escalation) and Part 2 (dose expansion). Only part 1 included in this analysis plan.

The first part of the study is dose escalation where cohorts of patients 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 et al, 2015) design will be utilized. 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 et al, 2017). This study is designed targeting a dose-limiting toxicity (DLT) rate of 25% with an equivalence interval of 20% to 30%.

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, patients 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.

The overall study schema of part 1 is presented in Figure 1

Figure 1 Study Schema



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.

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.

2.3. Determination of Sample Size

2.3.1. 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 may 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.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

Data analyses will be based on the analysis sets defined below. Unless otherwise specified, analyses will be conducted on the basis of first dose of study drug that a patient received.

3.1.1. All Subjects Set

All patients who signed the informed consent.

3.1.2. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least 1 dose of study drug (HMPL-306). This is the primary analysis set for safety and efficacy analyses.

3.1.3. DLT-Evaluable Analysis Set

The DLT- evaluable analysis set will be determined based on the medical review.

DLT analysis for the Part 1 dose escalation phase will be performed using the DLT evaluable analysis set.

3.1.4. Response Evaluable Analysis Set

The response evaluable analysis set will include all patients who are in the safety analysis set and have a measurable lesion at the baseline tumor assessment, and either (i) have at least 1 post-dose tumor assessment, or (ii) do not have post-dose tumor assessment but have clinical progression as noted by the investigator, or have died before their first post-dose tumor scan. The response evaluable analysis set will be used for analyses of anti-tumor response.

3.2. Protocol Deviation

All major and minor protocol deviations will be reviewed prior to final database lock. Only major protocol deviation will be summarized and all protocol deviations will be listed.

4. ENDPOINTS

4.1. General Principles for Derived and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

Reference start date is defined as the first date when a non-zero dose of study drug was administrated (first administration/dose date). Day 1 is the day of the first dose of study treatment in Cycle 1.

Study day will be calculated from the reference start date, and it will be used to show start/stop day of assessments and events relative to the first administration of study treatment.

- If the date of the event is on or after the reference start date, Study day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date, Study day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Reference end date is defined as the last date when a non-zero dose of study drug was administered.

4.1.2. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment prior to or on the first administration of study drug, including scheduled and unscheduled visits, unless otherwise specified. For quantitative measurements,

- change from baseline (CFB) will be calculated as: CFB = assessment value at visit X – baseline value;
- percentage CFB (% CFB) will be calculated as % CFB = (assessment value at each visit X – baseline value)/baseline value × 100.

4.1.3. Treatment Period

Unless otherwise specified, the treatment period is defined as the period prior to or on the date of first administration of study drug to 30+7 days (7-day window only replies to parameters collected by visit) after the date of last administration of study drug or prior to the start of a subsequent anti-tumor therapy (whichever comes first). For safety data, only the assessments/events collected during the treatment period will be summarized.

The worst post baseline is defined as the worst assessments/events during the treatment period including both scheduled and non-scheduled visit.

4.2. Efficacy Endpoints

4.2.1. Secondary Endpoints

4.2.1.1. Best Overall Response

BOR will be determined using time point responses (TPRs) up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or RANO criteria for glioma patients, or death; or (ii) withdrawal of consent or lost to follow-up; or (iii) receiving subsequent anti-cancer medications, whichever is earlier.

The timing of an overall TPR will always be derived based on scan dates, not response assessment dates. For a scheduled tumor scan assessment, it is expected that there may be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the overall response assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the same target lesions, the last assessment will be used.

BOR as defined by RECIST:

A patient's BOR will be determined based on Table 2.

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized.

Table 2 Best Overall Response When Confirmation of CR and PR are Required

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR

NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD

CR = Complete Response; NE = Not Evaluable; NA = Not Available; ORR = Objective Response Rate; PD = Progressive Disease; PR= Partial Response; SD = Stable Disease.

[a]The minimum interval for confirmation of CR and PR is 4 weeks.

[b]Best response will be SD if the first time point overall response is after 49 days on study. Otherwise, the best response will be PD.

[c]Best response will be SD if the first time point overall response if after 49 days on study. Otherwise, the best response will be NE.

[d]Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the patient is on study for a minimum of 49 days (counted from Cycle 1 Day 1). If the patient is on study for less than 49 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^ Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between CRs or PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

BOR as defined by RANO (for glioma patients):

The BOR was the best response among all the available time point responses (TPRs), the category of TPRs includes CR, PR, MR, SD, PD, and NE, and the order of the response is CR>PR>MR>SD>PD>NE. The hierarchical algorithm of deriving BOR category is detailed below.

- CR = at least one determination of CR. For example, a patient with 3 TPRs being CR, MR, and SD, then the BOR for this patient is CR.
- PR = at least two consecutive determinations of PR at least 4 weeks apart and before first documented PD or PR being the first response and being sustained for at least 4 weeks. For the consecutive determination of PR, the subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE, SD, or MR (e.g., PR NE PR, PR SD PR, or PR MR PR). However, only one (1) intervening NE, SD, or MR will be allowed between PRs for confirmation, that is, in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR. For PR being the first response, one intervening NE can be allowed before the response of PR, that is, in the response sequence of NE PR, the PR can also be considered as the first reported response.

  For example, (i) consecutive determinations of PR: a patient with 3 TPRs being PR, PR, and SD, and the duration between the two PRs is 6 weeks, then the BOR for this patient is PR; (ii) PR being the first response: a patient with 3 TPRs being PR, MR, and SD, and the duration between first dose date and the PR is 5 weeks, then the BOR for this patient is PR; a patient

with 2 TPRs being SD, PR, then the PR will downgraded to MR, hence, the BOR will be MR.

- MR = at least one determination of MR or not qualifying for PR criteria given that there are TPRs being PR. For example, (i) a patient with 3 TPRs being MR, SD, and SD, then the BOR for this patient is MR; (ii) a patient with 2 TPRs being SD and PR, however, the PR did not meet the criteria for BOR being PR, then the PR will be downgraded to MR, hence, the BOR for this patient will be MR.
- SD = at least one SD assessment or better before first documented PD (and not qualifying for CR, PR, MR, and PD). For example, a patient with 3 TPRs being SD, NE, and PD, then the BOR for this patient is SD.
- PD = PD after the first dose date and not qualifying for CR, PR, MR, and SD.
- NE = all other cases but patients are evaluable

The number and percentage of patients in each category of derived BOR (CR, PR, MR, SD, PD, or NE) will be summarized.

4.2.1.2. Objective Response Rate, and Disease Control Rate

Objective response rate (ORR) by RECIST will be calculated using two different ways:

- Scenario #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with confirmed objective response being "Yes".
- Scenario #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with unconfirmed objective response being "Yes".

Both ways (confirmed and unconfirmed) of assigning BOR will be implemented.

ORR defined as the proportion of patients with a confirmed BOR of complete response (CR) or partial response (PR) as determined by the investigator using RECIST v1.1.

ORR by RANO is defined as the proportion of patients with a BOR of complete response (CR) or partial response (PR) or MR as determined by the investigator using RANO.

Disease control rate (DCR) by RECIST is defined as the proportion of patients with a BOR of CR, PR, or SD lasting at least 7 weeks as determined by the investigator using RECIST v1.1.

DCR by RANO is defined as the proportion of patients with a BOR of CR, PR, MR, or SD lasting at least 7 weeks as determined by the investigator using RANO criteria for glioma patients.

4.2.1.3. Duration of Response

Duration (months) of response (DoR) by RECIST is defined as the time from the first occurrence

of confirmed PR or confirmed CR by RECIST v1.1, until disease progression or death, whichever comes first. Only those patients with objective responses of confirmed CR or confirmed PR will be included in this analysis.

DoR by RANO is defined as the time from the first occurrence of CR or PR or MR by RANO, until disease progression or death, whichever comes first. Only those patients with objective responses of CR or PR will be included in this analysis.

The DoR is calculated as (date of death or PD or last assessment – date of first occurrence of CR or PR or MR + 1)/30.4375. Censoring will follow the rules outlined for PFS in Table 3.

Table 3 Outcome and Event or Censoring Dates for Duration of Response

Rule	Situation	Date of Event or Censoring	Outcome
1	PD documented from schedule tumor assessment visits	Date of first documented PD	Event
2	Death without PD or death after one missing tumor assessment visit	Date of death	Event
4	No death or PD by the time of data cut-off for analysis	Date of last adequate tumor assessment prior to or on analysis data cutoff date	Censored
5	Early discontinuation (lost to follow-up or withdrawal of consent) of study without death or PD	Date of last adequate tumor assessment	Censored
6	New anti-tumor therapy started prior to PD	Date of last adequate assessment prior to or on date of initiation of new therapy visit	Censored
7	Death or PD after two or more consecutive missed or inadequate tumor assessment visits	Date of last adequate tumor assessment prior to missed visits	Censored

Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer medication occur on the same day, will assume that the progression was documented first, e.g. outcome is progression and the date is the date of the assessment of progression

Determination of two or more consecutive missing or inadequate assessments

In the derivation of duration of response, if a patient has a tumor assessment after two or more consecutive missed or inadequate tumor assessments, the patient will be censored at the last adequate tumor assessment. The following provides the rules for determining whether two or more consecutive tumor assessments are missed, of note, the relative day in the rules refers to the first dose date of study drug.

– If the tumor assessment date is prior to day 1 of week 17 (relative day < (16 + 1)×7 + 1 = 120), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment ≥ 126 days (=2* (8 weeks *7 + 7)), then the tumor assessment is considered as occurring after two or more consecutive missing tumor assessments;

– If the tumor assessment date is between day 1 of week 17 and day 1 of week 25 (relative day between (16 + 1)×7 + 1 = 120 and (24 + 1)×7 + 1 = 176), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment ≥ 161 days (= (8 weeks * 7 + 7 + 12 weeks * 7 + 2 weeks * 7)), then the tumor assessment is considered as occurring after two or more consecutive missing tumor assessments;

– If the tumor assessment date is on or after day 1 of week 25 (relative day ≥ (24 + 1)×7 + 1 = 176), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment ≥ 196 days (= 2* (12 weeks * 7 + 2 weeks * 7)), then the tumor assessment is considered as occurring after two or more consecutive missing tumor assessments.

Reasons for censoring are included in Table 4 following the hierarchy.

Table 4 Duration of Response Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	New anti-tumor therapy started prior to PD	New anti-tumor therapy started prior to PD
2	Two or more consecutive missed or inadequate radiological assessment visits	Two or more consecutive missed or inadequate radiological assessment visits
3	Drops out before end of study, no PD or death, lost to follow-up	No death nor PD, lost to follow-up
4	Drops out before end of study no PD or death, withdrawal by subject from the study	No death nor PD, withdrawal by subject
5	No death nor PD by the time of data cut-off for the analysis	No death nor PD by the time of data cut-off for the analysis

4.2.1.4. Time-to-response

Time (months) to response (TTR) by RECIST is defined as the time from start of study treatment until the date of first documented objective response, either confirmed CR or confirmed PR (whichever status is recorded first), according to RECIST v1.1. It will be calculated for patients whose BOR is either confirmed CR or confirmed PR.

TTR by RANO is defined as the time from start of study treatment until the date of first documented objective response, either CR or PR or MR (whichever status is recorded first), according to RANO. It will be calculated for patients whose BOR is either CR or PR or MR.

TTR is calculated as (date of first occurrence of CR or PR or MR – date of start of study treatment + 1)/30.4375.

4.2.1.5. Progression-free Survival

PFS is defined as the time (months) from the date of first administration of study treatment until the first radiographic documentation of objective progression as assessed by investigator using RECIST v1.1 or RANO criteria for glioma patients, or death from any cause.

More specifically, PFS will be determined using all the assessment data up until the last evaluable

visit prior to or on the date of

(i) disease progression as defined by RECIST Version 1.1 or RANO or death; or

(ii) withdrawal of consent or lost to follow-up; or

(iii) receiving subsequent anti-cancer medication, whichever is earlier.

Patients without report of PD or death from any cause at the time of analysis are censored as described in Table 5 below.

The PFS time will always be derived based on scan dates not tumor assessment dates. RECIST or RANO assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- Date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient is censored at the latest of the dates contributing to a particular overall visit assessment.

Table 5 Outcome and Event or Censoring Dates for PFS

Rule	Situation	Date of Progression or Censoring	Outcome
1	PD documented from radiological assessment visits	Date of first documented disease progression	Event
2	Death without PD or death after one missing radiological assessment visit	Date of death	Event
3	No baseline nor post-baseline radiological assessments available	Date of first administration of study treatment	Censored
4	No death or PD by the time of data cut-off for analysis	Date of last adequate radiological assessment	Censored
5	Early discontinuation (lost to follow-up or withdrawal of consent) of study without death or PD	Date of last adequate radiological assessment	Censored
6	New anti-tumor therapy started prior to PD	Date of last adequate radiological assessment prior to or on date of initiation of new therapy visit	Censored
7	Death or PD after two or more consecutive missed or inadequate radiological assessment visits	Date of last adequate radiological assessment prior to missed visits	Censored

Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer medication occur on the same day, will assume that the progression was documented first, e.g. outcome is progression and the date is the date of the assessment of progression

Note: The same algorithm for determination of two or more consecutive missing or inadequate assessments can be found in Section 4.2.1.3.

PFS is calculated as (date of progression or censoring as per rules in Table 5 – date of first administration of study treatment + 1)/30.4375. Reasons for censoring are included in Table 6 following the hierarchy.

Table 6 PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No baseline nor post-baseline tumor assessments available	No baseline nor post-baseline tumor assessments
2	New anti-tumor therapy started prior to PD	New anti-tumor therapy started prior to PD
4	Two or more consecutive missed or inadequate radiological assessment visits	Two or more consecutive missed or inadequate radiological assessment visits
5	Drops out before end of study, no progression or death, lost to follow-up	No death nor PD, lost to follow-up
6	Drops out before end of study no progression or death, withdrawal by subject from the study	No death nor PD, withdrawal by subject
7	No death nor PD by the time of data cut-off for the analysis	No death nor PD by the time of data cut-off for the analysis

4.2.2. Exploratory Endpoint

4.3. Exposure Endpoints

Duration of Exposure

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

In dose escalation, dose 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.

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

The duration of exposure (days) = Last dose date of non-zero study drug – first dose date of non-zero study drug + 1.

The actual duration of exposure (days) = Cumulative days with non-zero study drug administered.

Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 7.

Table 7 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	HMPL-306 CCI mg §
Dosing schedule per protocol	PO, QD, each day in a 28-day treatment cycle
Cumulative dose (mg)	Sum of the doses administered to a patient in the duration of exposure
Dose intensity (mg/day)	Cumulative dose (mg) / (duration of exposure)
Relative dose intensity (RDI) (%)	100 * [Dose intensity (mg/day) / (CCI) (mg/day)]

§ Different doses (e.g. CCI mg PO QD, CCI mg PO QD) of HMPL-306 may be evaluated. The calculation of relevant parameters will be adjusted accordingly based on the example presented in this table.
PO = *Per os* (oral administration); QD = *Quaque die* (once daily)

In addition, the RDI (%)will be categorized to the groups: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.

Dose Interruptions, and Dose Reductions

- Dose interruption and dose reductions are all based on the dose administration data, the associated reasons for each of them include categories: (1) Adverse event, (2) DLT, and (3) Other.
- Dose modifications of study drug include dose interruption and dose reduction.

4.4. Safety Endpoints

The safety analysis set is used to evaluate the safety variables including AEs, clinical laboratory data, vital signs, single 12-lead ECG parameters, ECHO/MUGA parameters, physical examinations, ECOG performance status, and death. The safety data during the treatment period will be summarized, and the treatment period is defined as the duration from the date of the first study drug administration until 30+7 days (7-day window only applied to parameters collected by visit) after last dose or prior to the start of a subsequent anti-tumor therapy (whichever comes first). Dose Limiting Toxicities (DLTs)

AEs will be assessed per the DLT criteria during the 28-day DLT assessment window in Cycle 1 for study Part 1, which starts with the first day of administration of study drug. .

4.4.1. Adverse Events (AEs)

All AEs will be coded from verbatim text to preferred term (PTs) and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. AEs will be graded by investigator according to NCI CTCAE v5.0. Missing severity grade will not be imputed.

An AE is considered a TEAE:
(i) If one of the criteria is met:

1. If the onset date is on or after the start of study treatment until 30 days after the last dose or prior to the start of a subsequent anti-tumor therapy (whichever comes first), or if the onset date is missing; or
2. If the AE has an onset date before the start of study treatment, but worsened in severity after the study drug administration (i.e. SAE start date is on or after the start of study treatment until 30 days after the last dose or prior to the start of a subsequent anti-tumor therapy (whichever comes first));

(ii) Beyond 30 days after the last dose or after the start of a subsequent anti-tumor therapy (whichever comes first), treatment-related SAEs will also be considered as TEAEs.

Investigator assessed AEs causality to study drug will be classified as "Related" and "Not Related". An AE with a missing causality will be classified as "Related" to study drug.

Other AE variables include drug-related AEs, COVID-19 related AEs, AEs leading to study drug modifications (i.e. dose interruption, dose reduction, or study drug withdrawal), AEs leading to death, and SAEs.

For AEs which are not on-going, duration of AE (days) is defined as AE end date – AE start date +1; for on-going AEs, the end date will be listed as 'Ongoing'.

4.4.2. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 8 will be measured.

Table 8 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC), platelet counts, ARC, Reticulocyte %, ANC, Neutrophils %, ALC, Lymphocytes %, Monocyte Absolute, Monocytes %, Basophil Absolute, Basophils %, Eosinophil Absolute, Eosinophils%, and other non-protocol specified tests
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, direct bilirubin, indirect bilirubin, calcium, magnesium, chloride, creatinine, creatine phosphokinase, glucose, inorganic phosphorus, potassium, total protein, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN), and other non-protocol specified tests
Blood amylase and lipase	amylase, lipase
Fasting lipid panel	Total Cholesterol, High-density Lipoprotein, Low-density Lipoprotein, Triglycerides
Coagulation	Activated Partial thromboplastin time (aPTT), Prothrombin time (PT), International normalized ratio (INR)
Urinalysis	semiquantitative dipstick: evaluation of glucose, protein, RBC, WBC, Ketone body, Urobilinogen

Change from baseline in laboratory test results to each assessment will be calculated. The non-protocol specified scheduled tests will not be summarized; they will only be included in listings. Data recorded by the laboratory will be converted to the International System of Units (SI) and all presentations will use SI units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Clinical laboratory results will be graded according to NCI CTCAE criteria, Version 5.0 which can be found in Appendix 1. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required. Grade 0 is assigned to all laboratory values except missing values and not already assigned another grade. Missing values are considered missing.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all assessments in treatment period.

- Aspartate aminotransferase (AST) > 3,5,8,10, and 20x ULN
- Alanine aminotransferase (ALT) > 3,5,8,10, and 20x ULN
- AST and/or ALT > 3,5,8,10, and 20x ULN
- Total bilirubin elevations > 1.5x, >=2x ULN
- ALP >1.5×, 2 × ULN
- AST and/or ALT > 3x ULN and (total bilirubin > 1.5×, >=2x ULN) [defined as at least one total bilirubin > 1.5×, >= 2x ULN within 14 days after ALT or AST > 3x ULN]
- Hy's Law criteria: AST and/or ALT > 3x ULN and total bilirubin ≥ 2x ULN and ALP < 2x ULN [defined as at least one total bilirubin >= 2x ULN and all ALP <2x ULN within 14 days after ALT or AST > 3x ULN]

Additionally, the minimum, and maximum values for each patient over the entire treatment period for each quantitative laboratory parameter will also be derived. The change from baseline will also be calculated using these minimum and maximum values.

All laboratory results in SI units are presented in data listings.

4.4.3. ECG

Electrocardiogram (ECG) parameters include heart rate, RR interval, PR interval, QT interval, QRS interval, QTcF intervals. Change from baseline to each post-baseline visit will be calculated. For a summary of ECG parameters, both the single 12-lead ECG data and the ECG triplicate assessments on Day 1 of Cycle 1 and Cycle 2 will be included. For the ECG triplicate assessments at a timepoint, the average of the triplicate assessment will be derived to represent the assessment at the timepoint. An overall ECG interpretation include the following categories: Abnormal, clinically significant; Abnormal, not clinically significant ; Normal; and Unknown.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 9.

Additionally, the minimum, and maximum values for each patient over the entire treatment period for each ECG parameter will also be derived. The change from baseline will also be calculated using these minimum and maximum values.

Table 9 Potentially Clinically Significant Criteria for ECG

ECG Parameter (unit)	Criterion value
Heart Rate (bpm)	>120

ECG Parameter (unit)	Criterion value
	<50
PR Interval (ms)	≥ 210
RR Interval (ms)	> 1200
	< 500
QRS Interval (ms)	≥ 120
	≤ 50
QT Interval (ms)	≥ 500
	≤ 300
QTcF (ms)	> 450
	> 480
	> 500
	≤ 300
	Increase from baseline > 30
	Increase from baseline > 60
	> 450 and increase from baseline > 30
	> 450 and increase from baseline > 60
	> 480 and increase from baseline > 30
	> 480 and increase from baseline > 60
	> 500 and increase from baseline > 30
	> 500 and increase from baseline > 60

4.4.4. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, respiratory rate, heart rate, body temperature, weight, Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 10.

Additionally, the minimum, and maximum values for each patient over the entire treatment period for each vital sign parameter will also be derived. The change from baseline will be calculated using these minimum and maximum values.

Table 10 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value
SBP (mmHg)	≥160 ≥180 ≤90 ≥180 and an increase ≥20 from baseline
DBP (mmHg)	≥105 ≤50 ≥105 and an increase ≥15 from baseline
Temperature (°C)	≥38.5 ≤35.5
Pulse rate (beats/min)	≥120 ≤50

Vital signs are listed by patient and visit.

4.4.5. Performance Status

ECOG performance status is to be summarized descriptively using counts and percentages by visit. In addition to the collected ECOG score during a Cycle, the maximum post-baseline value for a patient will be derived; both scheduled and unscheduled assessments will be used to identify the maximum post-baseline values.

4.4.6. Echocardiogram

ECHOs are performed at Screening, cycle 2 day 1, cycle 3 day 1, and then on day 1 of every odd cycle thereafter. Assessment parameters include left ventricular ejection fraction and overall interpretation of cardiac function. MUGAs are permitted if ECHOs cannot be performed.

4.4.7. Physical Examination

A comprehensive physical examination at Screening includes patient general appearance, eyes, ears, nose and throat, head and neck, respiratory, cardiovascular, abdomen (gastrointestinal), skin, mucous membranes, genitourinary system, lymph nodes, musculoskeletal, neurological, renal assessments.

Limited physical examination at scheduled visits is a subset the comprehensive physical examination as deemed appropriate by the investigator.

Results of physical examination are listed by patient and visit.

4.4.8. 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 study schedule of assessments. 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 adverse event (AE) related to HMPL-306, the frequency of the examination should be increased to once every cycle until the AE is relieved or stable.

5. ANALYSIS METHODS

5.1. General Principles

5.1.1. General Methodology

In general, all efficacy, and safety variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (observed number (n), mean, standard deviation, minimum, 25% percentile (Q1), median, 75% percentile (Q3), and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Time to event variable will be analyzed using Kaplan-Meier method and summarized with median, 25% and 75% percentiles with their corresponding 95% confidence intervals (CI) which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). Individual data will be presented in patient listings.

Analyses will be implemented using Enterprise® Version 8.3or higher (SAS Institute, Cary, North Carolina, USA).

Unless otherwise specified, analyses will be summarized:

- Efficacy analysis: by dose level and by disease type（glioma grade(Grade 2,3,4,2/3, Total) and different solid tumor type）.
- Analysis besides efficacy: by dose level/total and by disease type (glioma, non-glioma).

Analysis will be conducted on the basis of first dose of study drug that a patient received.

Hence, all summary tables, listings, and figures (TLFs) will be presented by dose/disease cohorts as defined in Table 11.

Table 11 Group Display in TLFs

Part of the study	Group	Group Description in Data Display
Part 1 - Dose Escalation	1	Cohort 1- [redacted]mg
	2	Cohort 2- [redacted]mg
	3	Cohort 3- [redacted]mg
	4	Cohort 4- [redacted]mg
	5	Cohort 5- [redacted]mg
	6	Cohort 6- [redacted]mg
	7	Cohort 7- [redacted]mg
	8	Cohort 8- [redacted]mg

For continuous data, unless otherwise specified, the mean, median, Q1, and Q3 will be presented with 1 more significant digit than the original values, and standard deviation and standard error (SE) will be reported with 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. The derived variables

will be presented with 1 decimal place. Percentages will be reported with 1 decimal point; if the count is 0, no percentage will be presented. Any rounding will be done after all calculations are made.

5.1.2. Handling Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only.

However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. The specific imputation rules are provided below, refer to Section 5.1.2.1 for the method of imputation of missing AE onset and stop date and Section 5.1.2.2 for the method of imputation of missing concomitant onset and stop dates. However, the imputed dates should not be shown in listings.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Unless otherwise specified, patients with missing data will be excluded only from analyses for which data are not available.

5.1.2.1. Adverse Events Start/End Date

AEs with onset/end dates that are partially/completely missing will be imputed as follows.

(i) AE start date:

- If the AE onset date is completely missing, the AE start date will be imputed as the reference start date;
- If the AE onset date is partial missing, then
  - If both the year and the month are available and the year and the month are the corresponding year and month of the reference start date, then the AE start date will be imputed as the reference start date;
  - If both the year and the month are available and the year and the month are not equal to the corresponding year and month of the reference start date, then the AE start date will be imputed as the 1st day of the month;
  - If only the year is available and the available year is the corresponding year of the reference start date, then the AE start date will be imputed as the reference start date;
  - If only the year is available, and the available year is not equal to the corresponding year of the reference start date, then the AE start date will be imputed as the January 1st of the year

(ii) AE end date will be imputed as below for the partial date only, the imputation rules only apply when the AE is not ongoing:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.

If the imputed AE end date is after the death date for patients is know to be dead at end of study or cut off date, the date of the death will be used for AE end date. If the imputed AE end date is after the last known alive date for patients alive at the end of study or cut off date, the date of last known alive date will be use for AE end date.

For AE continuing at the cut-off date, the end date will not be imputed and instead will be reported as "ongoing".

5.1.2.2. Concomitant Medication/Procedure/Surgery Start/End Date

Concomitant Medication/Procedure/Surgery with onset/end dates that are partially/completely missing will be imputed as follows.

(i) start date:

- 1st day of the month will be used to impute the start date if only the day is missing
- January 1st will be used to impute the start date if both the day and month are missing
- If the date is completely missing, then the day before the reference start date will be imputed as the start date.

(ii) end date:

- Last day of the month will be used to impute the end date if only the day is missing
- December 31st of the year will be used to impute the end date if both the day and month are missing
- If the date is completely missing, assign 'continuing' status to the end date

If the imputed start date is after the end date, the start date will be imputed as the end date. If the imputed end date is after the death date or last known alive date, the date of the death or last known alive date will be imputed as the Concomitant medication/procedure/surgery end date.

5.1.2.3. Date of Death

When a partial death date is reported, below rules will be used:

- If only the day of the month is missing, then date of death will be imputed as 1st of the month.

If the imputed date of death is earlier than EOS date, then date of death will be replaced by EOS date.

5.1.2.4. The Last Dose Date of Study Drug

When a partial last dose date of study drug is reported, below rules will be used:

- If only the day of the month is missing, then it will be imputed as the last day of the month;
- If both the day and the month are missing, then it will be imputed as the December 31st of the year
- If the imputed last dose date of study drug is later than date of death (if the subject died) / last known alive date (if the subject is not known to die) / EOT date / EOS date, data cut off date, then it will be replaced by the earliest of the above.

If the last dose date of study drug is complete missing, then it will be imputed by the earliest of the above.

5.1.2.5. Initial Diagnosis Date

When a partial initial diagnosis date is reported, below rules will be used:

- If the date is completely missing, do not impute;
- If both the day and the month are missing, then it will be imputed as July 1st of the year;
- If only the day of the month is missing, then it will be imputed as 15th of the month.

If the imputed initial diagnosis date is later than the first dose date of study drug, it will be replaced by the first dose date of study drug.

5.1.2.6. Subsequent Anti-cancer Therapy Date

When a partial subsequent anti-tumor therapy start date is reported, every effort will be made to identify the precedence relationship of starting date of subsequent anti-tumor therapy relative to the reference end date. Below rules will be used:

- If the date is completely missing, subsequent anti-tumor therapy date will be imputed as reference end date + 1;
- If only the day is missing, 15th day will be imputed as the subsequent anti-tumor therapy date;
- If both the day and the month are missing, then July 1st will be imputed as the subsequent anti-tumor therapy;

If the imputed date is earlier than reference end date, then it will be replaced with reference end date + 1, if the imputed date is later than the date of death or last known alive date, it will be replaced with the date of death or last known alive date.

5.1.2.7. Primary Diagnosis Date and Metastatic Disease Diagnosis Date

When a partial date of primary diagnosis or a partial date of first metastatic disease diagnosis is reported, the below imputation rules will be used:

- If the date is completely missing, no imputation will be conducted;
- If only the day is missing, 15th day will be assigned;
- If both the day and the month are missing, then July 1st will be assigned.

Check that the imputed date is not on or after the informed consent date.

5.2. Analysis Methods

5.2.1. Patient Disposition

Summary of study disposition will be summarized:

- Number of patients who signed the informed consent
- Number of screen failures and reason for screen failures
- Number of patients who received study treatment

Based on safety analysis set, the following will be summarized by dose level/total and disease type:

- Patients still on study treatment
- Number and percentage of patients who discontinue the study drug
- Reason for study drug discontinuation
- Number of patients still on study
- Number and percentage of patients who discontinue the study
- Reasons for discontinuation of the study-

A separate table will be presented to show the patients included in each analysis set and proper reasons for exclusion from an analysis set.

Patient's discontinuation status and inclusion in analysis sets will be also listed.

5.2.2. Protocol Deviations

Major Protocol deviations will be summarized descriptively (frequency and percentage) for patients with at least one major protocol deviation by protocol deviation categories. A patient with multiple protocol deviations under the same category will be counted once per deviation category. The protocol deviation summary is based on the safety analysis set.

In addition, all protocol deviations will be presented in a by-patient listing.

5.2.3. Demographic and Other Baseline Characteristics

For the safety analysis set, demographic and other baseline characteristics, such as age (years) at informed consent date, age groups (<65 years, >=65 years), gender, child bearing potential (if female), race, ethnicity, region (North America, and Europe), country, baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2) calculated as baseline weight (kg)/ [baseline height (m)]^2, BMI category (<18.5, ≥18.5 and <24, ≥24 kg/m^2), and baseline ECOG status, will be summarized and listed.

5.2.4. Disease Characteristics

Oncology history will be summarized descriptively by dose/disease cohorts and overall for the safety analysis set for the following:

- Diagnosis

- Time (months) since First Diagnosis of disease: it is calculated as (date of first study treatment administration – date of first diagnosis of disease + 1)/30.4375
- IDH Mutation Status
- Anatomical location of Primary tumor
- Time (months) since Diagnosis of Locally advanced/metastatic disease (months) : it is calculated as (date of first study treatment administration – date of diagnosis of metastasis disease + 1)/30.4375;
- Prior Oncology Treatments (Prior Anti-cancer Medication, Prior Anti-cancer Radiotherapy, Prior Anti-cancer Procedures)

In addition, oncology history data will be presented in a by-patient listing.

5.2.5. Medical History

The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Medical history will be coded to SOC and PT using MedDRA version 27.1.

The number and percentage of patients with any past medical/surgical history within each SOC and PT will be provided by dose/disease cohorts and overall on the safety analysis set. The number and percentage of patients with any ongoing medical history will be summarized.

A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT).

Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

In addition, medical history data will be presented in a by-patient listing.

5.2.6. Prior and Subsequent Anti-cancer Therapy

Prior and subsequent anti-cancer therapy, including mediation, radiotherapy, and procedure or surgery, will be summarized descriptively for the safety analysis set.

5.2.6.1. Anti-cancer Medication

Prior anti-cancer medications are defined as those taken by the patient prior to the administration of study drug. Subsequent anti-cancer medications are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer medications will be coded to ATC therapeutic group (i.e. ATC Level 2) and PT using the WHO-DD Version Global B3 Sep 2024.

The prior anti-cancer medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer medications will be summarized.

All prior and subsequent anti-cancer medications will be presented in a by-patient listing.

5.2.6.2. Anti-cancer Radiotherapy

Prior anti-cancer radiotherapy is defined as those taken by the patient prior to the administration of study drug.

Subsequent anti-cancer radiotherapy is defined as those taken by the patient after the discontinuation of the study drug.

The number and percentage of patients with at least one prior anti-cancer radiotherapy will be summarized by anatomical site.

Similarly, the subsequent anti-cancer radiotherapy will be summarized by anatomical site.

All prior and subsequent anti-cancer radiotherapy will be presented in a by-patient listing.

5.2.6.3. Anti-cancer Procedure or Surgery

Prior anti-cancer procedure or surgery are defined as those taken by the patient prior to the administration of study drug. Subsequent anti-cancer procedure or surgery are defined as those taken by the patient after the discontinuation of the study drug.

Prior and subsequent anti-cancer procedure or surgery will be coded to SOC and PT using MedDRA 27.1 or higher.

The prior anti-cancer procedure or surgery will be summarized by presenting the number and percentage of patients by PT and ATC(i.e. ATC Level 2). Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer procedure or surgery will be summarized.

All prior and subsequent anti-cancer procedure or surgery will be presented in a by-patient listing.

5.2.7. Prior and Concomitant Medications

Prior and concomitant medications (CMs) will be coded to ATC therapeutic group (i.e. ATC Level 2) and PT using the WHO-DD Version Global B3 Sep 2024.

Medications taken and stopped prior to the first dose of study treatment are denoted “Prior”. Medications taken prior to the first dose of study treatment and continuing beyond the first dose of study treatment or those medications started on or after the first dose of study treatment but no later than 30 days after the last dose are denoted “Concomitant”. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

The prior medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for

that PT or ATC. Each summary will be ordered by descending order of incidence of ATC according to total column and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the concomitant medications will be summarized.

All prior and concomitant medications will be presented in a by-patient listing.

5.2.8. Prior and Concomitant Surgery/Procedures

Procedures or surgeries that occurs prior to the first dose of study treatment are denoted "Prior". Procedures or surgeries that occurs after first dose date but no later than 30 days after the last dose are denoted "Concomitant".

Prior and concomitant surgery/ procedures will be classified using the MedDRA version 27.1.

The prior and concomitant surgery/procedures will be summarized by presenting the number and percentage of patients by PT and SOC. Patients having the same surgery/procedure multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC according to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

All prior and concomitant surgery/procedures will be presented a by-patient listing.

5.2.9. Efficacy Analyses

The safety analysis set will be used for PFS, and the response evaluable analysis set will be used for anti-tumor responses such as BOR, DoR, DCR, and TTR. No formal hypothesis testing is planned for this study. Two-sided 95% confidence intervals (CIs) will be calculated in the applicable summary, unless otherwise specified.

5.2.9.1. Secondary Efficacy Analyses

The number and percentage of patients in each category of derived BOR (CR, PR, Unconfirmed CR, Unconfirmed PR, MR, SD, PD, or NE) will be summarized by dose/disease cohorts for the response evaluable analysis set. ORR and ORR regardless of confirmation will be summarized by dose/disease cohorts. The two-sided 95% CIs of ORR and ORR regardless of confirmation will be calculated using the Clopper-Pearson method for each dose/disease cohorts.

The DCR will be analyzed in a similar way as ORR.

Tumor evaluation data will be presented in listings.

Swimmer plot will be presented for the treatment duration and tumor responses, including length of treatment duration, radiologic response, treatment ongoing or not, and death.

For the time to event endpoints, such as PFS and DoR, the median, 25% and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI. For PFS, additionally, estimates will be provided for the PFS probability along with their 95% CIs which are calculated using linear transformation based on the method by Brookmeyer and Crowley (1982) at selected landmarks, for example, at 3, 6, 9, 12, and 18 months. The Kaplan-Meier plots will be

produced for PFS. The duration of follow-up will be calculated descriptively using the Kaplan-Meier method.

In order to assess duration of follow-up for PFS, Kaplan Meier estimates will be calculated in the same way as in their analysis, while using different censoring rule which reverses censoring indicator instead, i.e. patients who have event will be censored at the date of event. Patients who are censored will assigned as "event".

Waterfall plot will be presented to depict the tumor shrinkage of target lesions, presenting each patient best percentage change in tumor size as a separate bar by dose/disease cohorts for the response evaluable analysis set. The best percentage change in target lesion size is defined as the maximum decrease or minimum increase among the percent changes from baseline to all post baseline visits per patient. In addition, spider plot will be presented including each patient percentage change in sum of target lesions, best overall response by dose/disease cohorts for the response evaluable analysis set. For both waterfall and spider plots, all the tumor assessment data from target lesion will be used up until the last evaluable prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al., 2009) or RANO criteria for glioma patients, or death; or (ii) withdrawal of consent or lost to follow-up; or (iii) receiving subsequent anti-cancer medications, whichever is earlier.

5.2.10. Exposure of Study Treatment

Exposure of study treatment described in Section 4.3 (duration of exposure, actual duration of exposure, cumulative dose, dose intensity, relative dose intensity) will be summarized by dose/disease cohorts and overall.

The following summary for dose modification will be summarized by dose/disease cohorts and overall.

- Number of patients with any dose modification (including both drug interruption and dose reduction)
- Number of patients with any drug interrupted (number of patients experienced drug interruption and reasons for drug interruption
- Number of patients with any dose reduced (number of patients with any dose reduction and reasons for dose reduction

5.2.11. Safety Analyses

Safety data during the treatment period will be summarized. Treatment period is defined as the duration from the date of the first study drug administration until 30+7 days (7-day window only applies to parameters collected by visit) or prior to the start of a subsequent anti-tumor therapy (whichever comes first) after last study drug administration.

5.2.11.1. Dose-Limiting Toxicity (DLT)

DLT analysis will be performed for the Part 1 based on the DLT evaluable analysis set.

In addition to summarizing number and percentage of patients with DLTs, DLTs will also be summarized by SOC, PT, and highest CTCAE grade.

DLTs will be listed.

5.2.11.2. Adverse Events

An overall summary of the number and percentage of patients along with the number of adverse events will be provided for the following categories of AEs:

- Any TEAE
- Any TEAEs by maximum CTCAE grade
- Any TEAE of CTCAE Grade 3 or higher
- Any TEAE Leading to Dose Modification
    - Any TEAE Leading to Dose Reduction
    - Any TEAE Leading to Drug Interruption
- Any TEAE Leading to Drug Discontinuation
- Any TEAE Leading to Death
- Any Treatment Related TEAE
- Any Treatment Related TEAE of CTCAE Grade 3 or higher
- Any Treatment Related TEAE Leading to Dose Modification
    - Any Treatment Related TEAE Leading to Dose Reduction
    - Any Treatment Related TEAE Leading to Drug Interruption
- Any Treatment Related TEAE Leading to Drug Discontinuation
- Any Treatment Related TEAE Leading to Death
- Any Serious TEAE
- Any Treatment Related Serious TEAE
- Any Special Interest TEAE (AESI)
- Any Treatment Related AESI
- Patients with Any COVID-19-related TEAEs as well as CTCAE Grade 3 or higher

The following categories will be summarized (the number and percent of patients) by SOC, PT and maximum CTCAE grade (Grade 1/2, Grade ≥3, All Grade).

	Summary scope

TEAE	• Any TEAE
	• TEAEs with CTCAE grade 3 or higher (maximum CTCAE grade by Grade 3, Grade 4, Grade 5)
	• TEAEs leading to dose modification
	  ○ TEAEs leading to dose interruption
	  ○ TEAEs leading to dose reduction
	• TEAEs leading to discontinuation of study drug

	• TEAEs leading to death (by SOC and PT only)

Treatment-related TEAE	• Any treatment-related TEAE
	• Treatment-related TEAEs with CTCAE grade 3 or higher (maximum CTCAE grade by Grade 3, Grade 4, Grade 5)
	• Treatment-related TEAEs leading to dose modification
	  ○ Treatment-related TEAEs leading to dose interruption
	  ○ Treatment-related TEAEs leading to dose reduction
	• Treatment-related TEAEs leading to discontinuation of study drug
	• Treatment-related TEAEs leading to death (by SOC and PT only)

Serious TEAE	• All serious TEAE (Grade 1/2, Grade ≥3, All Grade, Related). • Treatment-related serious TEAEs
COVID-19-related TEAEs	• COVID-19-related TEAEs

In addition, all TEAE and treatment-related TEAE will also be summarized (the number and percent of patients) by PT and maximum CTCAE grade (All Grade, Grade ≥3, Grade 1/2).

If a subject experienced the same adverse event (as identified by MedDRA preferred term) more than once during the study, the worst occurrence (e.g. worst grade) will be counted. Similarly, if a subject experienced more than one occurrence of the same SOC/PT, the worst occurrence (e.g. worst grade) will be counted within a particular SOC/PT. When summarizing AE by CTCAE grade, if a subject experienced more than one occurrence of the same SOC/PT, the worst severity grade will be counted. Each summary will be ordered by descending order of incidence of SOC and PT within each SOC. If the frequencies of SOC/PT tie, an alphabetic order of SOC/PT will be applied.

AESI Summary

AEs of special interest (AESI) are listed in the below table, and will be identified by MedDRA Query (SMQ)/PT:

AESI	**Search Strategy**
Abnormal hepatic function	Drug related hepatic disorders - comprehensive search (SMQ Code 20000006 Narrow search)

Abbreviations: AESI = adverse event of special interest; PT = preferred term; SMQ = standard MedDRA query.

All AESIs will be summarized in frequency and percent by AESI category, PT and maximum CTCAE grade (All Grade, Grade ≥3, Grade 1/2). The followings will also be summarized for each AESI category:

- AESI
- Treatment Related AESI
- AESI of CTCAE Grade 3 or higher

- AESI meeting SAE criteria
- AESI leading to dose modification
- AESI leading to dose reduction
- AESI leading to dose interruption
- AESI leading to dose discontinuation
- AESI leading to death

Moreover, time to AESI onset (days), AESI duration (days) and AESI outcome (the number and percent of patients) will be summarized descriptively.
Time to AESI onset is defined as the time interval from the date of first dose of study drug to the earliest onset date among all AESIs. That is, if a subject has multiple AESI occurrences, the earliest AESI onset date will be used as the onset date to calculate time to onset of AESI.
AESI duration (days) will only be calculated for ended AESI as (AE end date-AE start date+1).

AE Listing

All AE will be listed.All AE information including AE term, start date, end date, severity, whether the AE is DLT, CTCAE grade, whether the AE is SAE, classification of SAE (if SAE), whether the AE is AESI, relationship to study drug, action taken, outcome, whether this event is considered as part of Differentiation Syndrome will be presented in subject data listings. If the AE is ongoing at the data cut-off date, it will be reported as 'Ongoing' in the listing.
In addition, separate listings of all SAEs, AESIs, AEs leading to death and AEs leading to discontinuation of study drug will be provided.

5.2.11.3. Death

Number of deaths and primary cause of death are summarized descriptively. Similarly, the deaths happening during the treatment period and follow-up period will also be tabulated.

Data of deaths will be provided as patient list in which the on-treatment death will be flagged.

5.2.11.4. Laboratory Evaluations

For selected quantitative laboratory test, the observed values and change from baseline will be summarized by scheduled visit using descriptive statistics. For selected qualitative laboratory test, number and percentage of patients with categorical results will be summarized for each scheduled visit. Toxicities for clinical labs will be characterized according to NCI CTCAE, v5.0 (Appendix 1 shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Shift table from baseline to worst post-baseline value according to abnormality (Normal / Abnormal, Not Clinically Significant / Abnormal, Clinically Significant) assessed by investigator will be provided.
The number and percentage of patients satisfying abnormal hepatic laboratory values categories defined in Section 4.4.2 will be summarized.
The frequency and percentage of patients with categories of abnormal hepatic laboratory values during the treatment period will be summarized.

Listings of all laboratory data with normal reference ranges, and CTCAE grades (when possible) will be provided.

5.2.11.5. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline by scheduled visit. Triplicate results will be averaged for tabulation.

The criteria for potentially clinically significant findings are defined in Table 9. The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

Shift table from baseline to worst post-baseline value according to abnormality (Normal / Abnormal, Not Clinically Significant / Abnormal, Clinically Significant) assessed by investigator will be provided.
A listing of all ECG data will be provided.

5.2.11.6. Vital Signs

For vital sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature, and Weight) the observed values and change from baseline will be summarized using descriptive statistics at each scheduled visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 10) during the overall treatment period will be presented.

Moreover, the minimum, and maximum, and their corresponding change from baseline vital sign values will be summarized descriptively overall treatment period.

A listing of all vital sign data will be provided.

5.2.11.7. Performance Status

The frequency and percentage of patients for each ECOG score level will be summarized by visit. Shift in grade from baseline to the maximum post-baseline score will be summarized.

A listing of ECOG score for all patients will be provided.

5.2.11.8. Echocardiogram

Descriptive statistics for Echocardiogram/MUGA will be summarized by scheduled visit. A by-patients listing of Echocardiogram/MUGA values at each time point will be listed.

Shift table from baseline to worst post-baseline value according to abnormality (Normal / Abnormal, Not Clinically Significant / Abnormal, Clinically Significant) assessed by investigator will be provided.

5.2.11.9. Physical Examination

A listing of physical examination data for all patients will be provided.

5.2.11.10. Ophthalmologic Assessments

A listing of ophthalmologic assessments data for all patients will be provided.

5.3. Subgroup Analyses

Not applicable.

5.4. Other Analyses

5.4.1. Gene Mutational Analysis

The number and percent of patients with gene mutation will be summarized by each mutation category. A listing of gene mutational data for all patients will be provided.

5.4.2. Pharmacokinetic Analysis

The detailed analysis will be described in a separate PK analysis plan which will also include the analysis for 2-HG.

5.4.3. 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. The detailed analysis will be described in a separate PK analysis plan

6. PLANNED ANALYSIS

6.1. 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.

6.2. Interim Analysis

No formal 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.

6.3. Final Analysis

The final analysis will be conducted after Database Lock (DBL) for this study.

7. CHANGE FROM THE PROTOCOL

Here is a list of changes in this analysis plan compared with the protocol

- The DLT- evaluable analysis set definition in the protocol is to include all patients enrolled into dose escalation part of the study who (i) either received at least 75% of assigned doses of the HMPL-306 during the DLT assessment window (i.e. Cycle 1 Day 1 [C1D1] through C1D28) or (ii) experienced a DLT in Cycle 1. However, since these criteria have been incorporated in the SRC review, the DLT-evaluable analysis set will be based on the decision from the SRC review.
- Though there is no protocol amendment, it was noted that the study did not proceed to the dose expansion part. That is, no patients were enrolled to the expansion cohorts A (cholangiocarcinoma), B (skeletal chondrosarcoma), C (low-grade glioma), C-1 (perioperative glioma), and D (any other solid tumor harboring an IDH mutation). Hence, the analysis of the study will be conducted only for the dose escalation part.
- DLT-equivalent summary was defined in the protocol, consider that DLT-equivalent event was not well collected in EDC, this summary will not be done.

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