STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Multicenter Study of HMPL-306 in Advanced Hematological Malignancies with Isocitrate Dehydrogenase (IDH) Mutations

Protocol Number:	2020-306-GLOB1
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

Date	Version	Description	Author
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LIST OF ABBREVIATIONS

Abbreviation	Term
2-HG	2-Hydroxyglutaric acid
AE	Adverse event
AESI	Adverse event of special interest
AITL	Angio-immunoblastic T-cell lymphoma
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ATC	Anatomic therapeutic classification
BMI	Body mass index
BP	Blood pressure
CBR	Clinical benefit rates
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CR_{MRD-}	Complete response with negative minimal residual disease
CRi	Complete response with incomplete count
CRh	Complete response with partial hematological recovery
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DBP	Diastolic blood pressure
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DOCR	Duration of CR
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ECHO	Echocardiogram
EFS	Event-free survival
GCP	Good clinical practice
ICH	International council on harmonization
IDH	Isocitrate dehydrogenase
IWG	International working group
LLQ	Lower limit of quantification
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
MLFS	Morphologically leukemia-free state
mTPI-2	Modified toxicity probability interval-2
MUGA	Multiple-gated acquisition
NCI	National cancer institute
MTD	Maximum tolerated dose
ORR	Objective response rate

Abbreviation	Term
OC	Observed case
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PO	Oral(ly)
PR	Partial response
PS	Performance status
PT	Preferred term
QD	Once daily
QTcF	QT interval corrected by the method of fredericia
RBC	Red blood cell
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
SD	Stable disease
SOC	System organ class
SRC	Safety review committee
TD	Transfusion dependence
TEAE	Treatment-emergent adverse event
TI	Transfusion independence
TPR	Timepoint response
TTCR	Time to CR
TTR	Time to response
WBC	White blood cell
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-GLOB1. The SAP is based on the Protocol Version Amendment 5 (dated 02 Nov 2023) and CRF version 8 (dated 11 Sep 2024).

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).

In the protocol, though patients with high-risk myelodysplastic syndrome (MDS) and angio immunoblastic T cell lymphoma (AITL) were also planned to be enrolled to the study, in reality, there were no patients with MDS and AITL enrolled into the study. Therefore, the analysis of the study will be focused only on AML patients from dose escalation part and dose expansion part.

The analyses related to pharmacokinetic (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

Tier	Objectives	Endpoints
Primary	**Part 1 – Dose Escalation:** To evaluate the safety and tolerability of HMPL-306 in patients with advanced hematological malignancies that harbor isocitrate dehydrogenase (IDH) mutations.	• Maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) • Safety including dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, electrocardiograms (ECGs), and clinical laboratory abnormalities
	Part 2 – Dose Expansion: To characterize safety and tolerability and to determine RP2D of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations.	• Safety including DLTs, TEAEs, SAEs, deaths, ECGs, and clinical laboratory abnormalities
Secondary	To assess preliminary antitumor activity of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations.	• Best overall response (BOR), objective response rate (ORR), time to response (TTR), duration of response (DoR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), disease free survival (DFS), event-free survival (EFS), and post-baseline transfusion independence
	To assess pharmacokinetics (PK) of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	• Observed plasma concentrations and drug exposure parameters of HMPL-306
	To assess pharmacodynamics (PD) of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	• Observed plasma concentrations of 2-hydroxyglutaric acid (2-HG)
Exploratory	To explore relationships between changes in frequency of genetic mutations, efficacy, PK, PD and safety after HMPL-306 treatment	• Changes from baseline in tumor markers, correlation with drug exposure, target engagement and efficacy and safety outcomes
	To explore relationships between HMPL-306 PK drug exposure, target engagement (TE), 2-HG levels, and percentage inhibition	

	To explore the influence of genetic abnormalities (other than IDH mutations) on safety, efficacy, PD, PK, and clinical response to HMPL-306 treatment.	

2-HG = 2-hydroxyglutaric acid; CBR=clinical benefit rate; DFS=disease-free survival; DLT = dose-limiting toxicity; DoR=duration of response; ECG = electrocardiogram; EFS=event-free survival; IDH = isocitrate dehydrogenase; MTD = maximum tolerated dose; ORR=objective response rate; OS=overall survival; PD = pharmacodynamics; PK = pharmacokinetics; PFS=progression-free survival; PR=partial response; RP2D = recommended phase 2 dose; SAE = serious adverse event; SD=stable disease; TEAE = treatment emergent adverse event; TTR=time to response.

2.2 Study Design

This is a phase 1, open-label, multicenter, single-arm study to evaluate safety, tolerability, PK, PD and preliminary efficacy of HMPL-306 administered orally in treatment of patients with advanced relapsed, refractory, or resistant hematological malignancies that harbor IDH mutations. The study consists of 2 parts: dose escalation part (Part 1) and dose expansion part (Part 2).

The first part of the study is dose escalation, where cohorts of patients will receive ascending oral doses of HMPL-306 to determine MTD and/or the RP2D. The modified toxicity probability interval-2 (mTPI-2) (Greenberg 2012, Guo 2017) design will be used to perform dose escalation and MTD/RP2D determination. Briefly, 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 (Greenberg 2012, Guo 2017). This study is designed targeting a DLT rate of 20% with an equivalence interval of 15% to 25%.

Seven days prior to initiating daily administration of HMPL-306 from Cycle 1 Day 1 (C1D1), patients enrolled in each cohort during dose escalation will be administered a single oral dose of HMPL-306 on Day -7 relative to C1D1 (Day 1 of PK week). Serial blood samples will be collected from Days 1 to 7 of the PK week for analysis of plasma concentrations of HMPL-306 and 2-HG.

A cycle of study treatment is defined as 28 days of continuous daily dosing. After the PK week, dose escalation will start at CCI mg QD orally (PO) for Cohort 1 and then escalate in 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.

Safety monitoring and evaluation of dose escalation will be carried out by the Safety Review Committee (SRC), which is comprised of the sponsor and investigators.

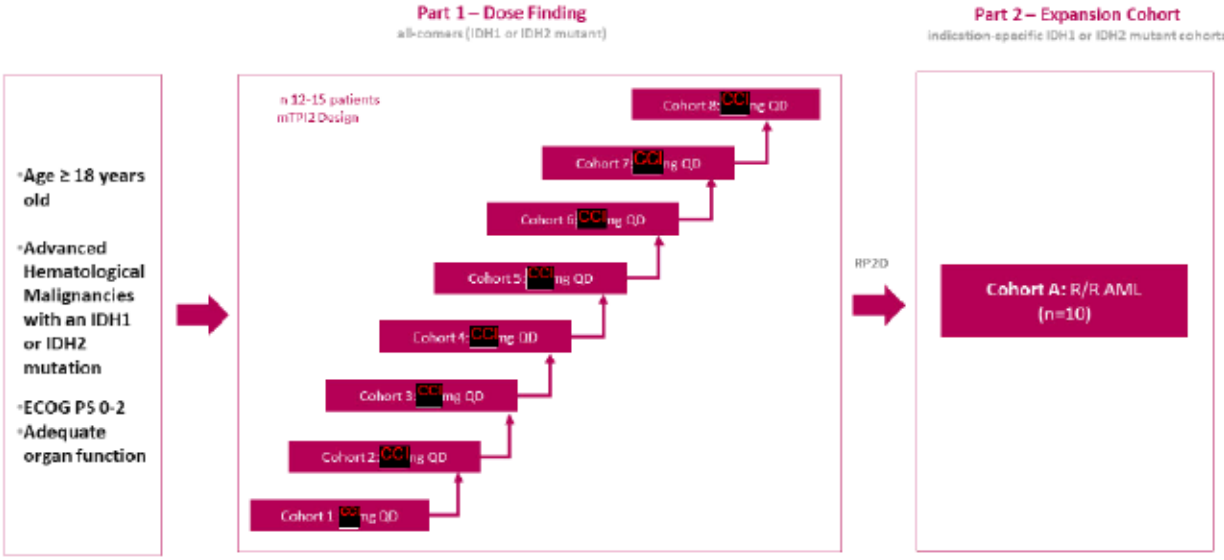
In the dose-expansion part, 1 cohort of patients will receive HMPL-306 at MTD and/or RP2D to evaluate further the safety, tolerability, PK, PD, and preliminary efficacy in approximately 10 patients with advanced relapsed, refractory, or resistant hematological malignancies with IDH mutations. Patients enrolled in the dose expansion part must not have standard therapeutic options available (including IDH inhibitors where approved) and must have the following:

- Relapsed AML unsuitable for intensive chemotherapy or venetoclax-based regimen or target agents;
- Primary refractory AML unsuitable for intensive chemotherapy or venetoclax-based regimen or target agents;
- Relapsed/refractory AML that has progressed on prior IDH treatment

The sponsor, in consultation with SRC, may decide to increase or decrease the number of enrolled patients in each cohort, depending on preliminary clinical response, safety signals, or operational feasibility. Patients who are not efficacy evaluable in any cohort may be replaced.

The overall study schema is presented in Figure 1.

Figure 1 Study Schema



Any patient who discontinues treatment should be encouraged to return to the study site for an End of Treatment (EOT) Visit and continue with the remaining study visits. Patients must be discontinued from treatment for disease progression, withdrawal of consent, intolerable toxicity, repeated non-compliance or poor compliance, commencement of other antitumor treatment during the study, pregnancy, loss to follow-up, termination of the study by the sponsor, death, or end of the study.

Patients 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 for tumor assessments and will be followed every 12 weeks (±14 days) from the EOT visit or last assessment, until disease progression, initiation of new anticancer therapy, withdrawal of consent, lost to follow-up, death, conditions are met, or the end of the study, whichever comes first. Survival information can be obtained via phone and information will be documented in the source documents and relevant case report forms (CRFs). The end of study is defined as the date on which all patients have their last visit or 1 year after the last patient has their first visit, whichever comes first.

2.3. Determination of Sample Size

Approximately 40 to 50 patients are to be enrolled in this study (approximately 24 to 30 evaluable patients are expected in the dose-escalation part and approximately 10 patients are estimated for the dose expansion part).

2.3.1. Dose Escalation Part

The maximum sample size in this part will be determined jointly by the sponsor and investigator. The exact sample size of mTPI-2 design in dose escalation part cannot be pre-specified due to dynamic nature of Bayesian allocation procedure. Patients not evaluable for DLT may be replaced, and this may result in the number of patients enrolled being more than expected. An estimated 24 to 30 evaluable patients may be enrolled in this part.

2.3.2. Dose Expansion Part

To better describe the safety of the recommended single-dose of HMPL-306 for future studies, approximately 10 AML patients are expected to be treated with HMPL-306 at this part. For a given adverse event (AE) with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 AE in 10 patients is 65%, 40%, and 9.6%, respectively.

Assuming that the true complete response (CR) rate is 20%, then the probability that at least 1 case of CR is observed in a cohort of 10 patients is 89%, the probability that at least 2 cases of CR are observed is 62.4%, and the probability that no CR is observed is 11%. If further evaluation of safety and efficacy signals is warranted, then more patients may be enrolled in the dose expansion cohort.

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 level of study drug that a patient received.

3.1.1. All Subject Set

All patients who signed the informed consent (including pre-screening and screening informed consent).

3.1.2. Safety Analysis Set

All enrolled patients who received at least 1 dose of study drug (HMPL-306) will be included in safety analysis population. This is the primary analysis set for safety analysis.

3.1.3. DLT-Evaluable Analysis Set

The DLT-evaluable analysis set includes all patients provided by HUTCHMED clinical team based on the decision made with the SRC after SRC meeting for each cohort during the dose escalation phase.

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

3.1.4. Efficacy Analysis Set

All enrolled patients who received at least 1 dose of study drug from C1D1 in continuous cycle (i.e. excluding single oral dose from the PK week for the dose escalation part) will be included in efficacy analysis population. This is the primary analysis set for efficacy analysis.

3.1.5. Response Evaluable Analysis Set

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

3.2. Protocol Deviation

Protocol deviations including deviations are recorded as outlined in the latest version of the Protocol Deviation and Non-compliance Management Plan. All major and minor protocol deviations will be reviewed and confirmed prior to final database lock.

4. ENDPOINTS

4.1. General Principles for Derived and Transformed Data

4.1.1. Reference Start Date and End Date and Study Day

(1) Reference start date

Dose escalation part:

For efficacy analysis, reference start date (Day 1) is defined as the first date when a non-zero dose of study treatment in continuous dosing cycle (i.e. excluding single oral dose from the PK week) is administrated.

For safety analysis, reference start date (Day 1) is defined as the first date when a non-zero dose of study treatment (i.e. including single oral dose from the PK week) is administrated.

Dose expansion part:

Reference start date (Day 1) is defined as the first date when a non-zero dose of study treatment is administrated.

(2) Reference end date

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

(3) Study day

Study day will be calculated from the reference start date, and it will be used to show start/stop day of assessments or events relative to the start date 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).

Note that, the day of the first dose of study drug is day 1 and the day before it is day – 1, not day 0.

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

4.1.2. Last known alive date

Last known alive date will be derived for patients not known to have died at the analysis cut-off date using the latest date (including complete date and partial date with Month and Year information) among the following data:

- All assessment / scan / sample collection dates (e.g., laboratory, vital signs assessments, ECG, eastern cooperative oncology group (ECOG), physical examinations, performance status assessment, tumor assessment dates, ophthalmologic examination, etc.).
- Medication dates, including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.
- Procedure dates, including concomitant procedures, anticancer radiotherapies / procedures taken after study treatment discontinuation, blood transfusion.
- Adverse events start and end date, date when AE became serious, hospitalization start and end date.
- Date latest contact collected on 'Survival Follow-up' or 'Efficacy Follow-up' page where subject status is 'Alive'.

4.1.3. Baseline and Change from Baseline

Baseline is defined as the last non-missing assessment on or prior to the first administration of study treatment, 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.

4.1.4. Treatment Period

Unless otherwise specified, the treatment period is defined as the duration from the date of the first study drug administration 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. Only the on-treatment safety assessments will be included in the summary tables.

4.2. Efficacy Endpoints

4.2.1. Best Overall Response

Assessment of anti-tumor response for patients with AML will be conducted according to 2017 European Leukemia Net (ELN) criteria (Döhner et al, 2017). Best overall response (BOR) is defined as the best response during the anti-tumor evaluation period, which will be determined using time point responses (TPRs) from date of the first dose of study treatment from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) up until the last evaluable TPR prior to or on the date of (i) disease progression (at least 2 cycles of study drug should be administered to determine PD) / relapse according to the 2017 ELN criteria, or death; or (ii) withdrawal of consent or lost to follow-up; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

The hierarchical order of these response categories is complete response with negative minimal residual disease (CR_{MRD-}) > complete response (CR) > complete response with partial hematological recovery (CRh) > complete response with incomplete count (CRi) > morphologically leukemia-free state (MLFS) > partial response (PR) > stable disease (SD) > progressive disease (PD) > NE (not evaluable), where CR_{MRD-}, CR and CRi are based on investigator assessment of response, and CRh will be derived from relevant data including investigator-collected bone marrow and hematology data by medical team as external file, as CRh is not defined in ELN 2017. This order will be used to derive the BOR. For example, a patient who has 4 anti-tumor assessments during the anti-tumor evaluation period with response being MLFS, PR, SD, and PD respectively, then the BOR for this patient will be MLFS.
Of note, for the BOR being SD, it is expected that the duration of SD lasts for at least 3 cycles, for example, if a patient only has one tumor assessment at 2 cycles with response being SD, then, the BOR for this patient will be NE instead. For the BOR being PD, at least 2 cycles of study drug should be administered, for example, if a patient only has one tumor assessment at 1 cycle of study drug with response being PD, then, the BOR for this patient will be NE instead.
Moreover, subjects who do not have post-dose tumor assessment, but have clinical progression as noted by the investigator or have died due to any cause before their second post-dose tumor assessment, BOR will be PD.

For patients whose BOR is 'NE', reasons for NE will be summarized as followings:

- All post-baseline overall responses are NE / No baseline or post-baseline assessments;
- Initiation of subsequent anti-tumor therapy prior to the first post-baseline tumor assessment;
- SD lasts less than 3 cycles;
- Less than 2 cycles of study drug to determine PD.

4.2.2. Composite Response, Objective Response Rate and Clinical Benefit Rate

Some composite response categories are defined as following based on BOR.

- Composite complete response (cCR)-1: including the response category of CR_{MRD-}, CR, CRh, and CRi;
- cCR-2: including the response category of CR_{MRD-}, CR and CRh;
- cCR-3: including the response category of CR_{MRD-} and CR;

CR rate by 24 weeks is defined as the proportion of patients with BOR being CR by 24 weeks during the tumor evaluation period. The protocol allows a 1-week window for disease assessments. Therefore, a patient will be considered to have achieved "CR by 24 weeks" if the date of first CR is within 25 weeks (24 weeks target+1week window) after the date of first study drug administration: CR by 24 weeks if date of first CR minus (–) date of first study drug administration + 1 ≤24×7+7. The cCR-1 rate by 24 weeks, cCR-2 rate by 24 weeks, and cCR-3 rate by 24 weeks will be similarly calculated.

Objective response rate (ORR) is defined as the proportion of patients with BOR being CR_{MRD-}, CR, CRh, CRi, MLFS, or PR.

Clinical benefit rate (CBR) is defined as the proportion of patients with BOR being CR_{MRD-}, CR, CRh, CRi, MLFS, PR, or SD lasting for 3 cycles.

4.2.3. Duration of Response

Some duration (months) of responses are defined as follows:

- Duration of CR (DOCR) is defined as the time from the first occurrence of CR until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with CR will be included in this analysis.
- Duration of CRh (DOCRh) is defined as the time from the first occurrence of CRh until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with CRh will be included in this analysis.
- Duration of cCR-1 (DOcCR1) is defined as the time from the first occurrence of cCR-1 until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with cCR-1 will be included in this analysis.
- Duration of cCR-2 (DOcCR2) is defined as the time from the first occurrence of cCR-2 until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with cCR-2 will be included in this analysis.
- Duration of cCR-3 (DOcCR3) is defined as the time from the first occurrence of cCR-3 until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with cCR-3 will be included in this analysis.
- Duration of objective response (DOOR) is defined as the time from the first occurrence of objective response (CR_{MRD-}, CR, CRh, CRi, MLFS, or PR) until disease progression, relapse, or death due to any cause, whichever comes first. Only patients with objective response will be included in this analysis.

The duration (months) of response is generally calculated as (date of death or PD or Relapse or last assessment – date of first occurrence of interested response category + 1)/30.4375. The rule of censoring will follow these rules outlined in Table 2.

Table 2 Outcome and Event or Censoring Dates for Duration of Response

Rule	Situation	Date of Event or Censoring	Outcome
1	Relapse (or PD) documented between schedule tumor assessment visits or after one missing tumor assessment visit	Date of first documented relapse (or PD)	Event
2	Death without relapse (or PD) between scheduled assessment visit or death after one missing tumor assessment visit	Date of death	Event

4	No death or relapse (or PD) by the time of data cut-off for final 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 relapse (or PD)	Date of last adequate tumor assessment	Censored
6	Subsequent anti-tumor therapy started prior to relapse (or PD) or death	Date of last adequate assessment prior to or on date of initiation of subsequent anti-tumor therapy	Censored
7	Death or relapse (or PD) after two or more consecutive missed or inadequate tumor assessment visits	Date of last adequate tumor assessment prior to missed visits	Censored

PD is only applicable for the duration of objective response.

Note: An adequate tumor assessment is defined as an assessment where the Investigator determined response is CR_{MRD-}, CR, CRh, CRi, MLFS, PR, SD, and PD. If PD and subsequent anti-cancer therapy 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.

(a) Determination of one missing or inadequate assessment

The following provides the rules for determining whether one tumor assessments is missed, of note, the relative day in the rules refers to the first dose date of study drug from Cycle 1 in continuous cycle.

- If the tumor assessment date is prior to day 1 of week 23 (relative day $< (24 - 1) \times 7 + 1 = 162$), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment $\geq$ 63 days (8 weeks *7 + 7), then the tumor assessment is considered as occurring after one missing tumor assessment;
- If the tumor assessment date is on or after day 1 of week 23 (relative day $< (24 - 1) \times 7 + 1 = 162$), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment $\geq$ 98 days (12 weeks *7 + 14), then the tumor assessment is considered as occurring after one missing tumor assessment.

(b) Determination of two or more consecutive missing or inadequate assessments

The following provides the rules for determining whether two or more consecutive tumor assessments are missed.

- If the tumor assessment date is prior to day 1 of week 15 (relative day $< (16 - 1) \times 7 + 1 = 106$), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment $\geq$ 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 15 and day 1 of week 23 (relative day between $(16 - 1) \times 7 + 1 = 106$ and $(24 - 1) \times 7 + 1 = 162$), and the difference between the tumor assessment date and the next adjacent adequate tumor assessment $\geq$ 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 23 (relative day ≥ (24 - 1)×7 + 1 = 162), 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 3 following the hierarchy.

Table 3 Duration of Response Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Subsequent anti-tumor therapy started prior to relapse (or PD) or death	Subsequent anti-tumor therapy started prior to relapse (or PD) or death
2	Death or relapse (or PD) after two or more consecutive missed or inadequate tumor assessment visits	Missed or inadequate two or more consecutive tumor assessment visits
3	Drops out before end of study, no relapse (or PD) or death, lost to follow-up	No death or relapse (or PD), lost to follow-up
4	Drops out before end of study no relapse (or PD) or death, withdrawal by subject from the study	No death or relapse (or PD), withdrawal by subject
5	No death or relapse (or PD) by the time of data cut-off for the analysis	No death or relapse (or PD) by the time of data cut-off for the analysis

PD is only applicable for the duration of objective response.

4.2.4. Time to Response

Some time (months) to responses are defined as follows:

- Time to CR (TTCR) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first CR. Only patients with CR will be included in this analysis.
- Time to CRh (TTCRh) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first CRh. Only patients with CRh will be included in this analysis.
- Time to cCR-1 (TTcCR1) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first cCR-1. Only patients with cCR-1 will be included in this analysis.
- Time to cCR-2 (TTcCR2) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first cCR-2. Only patients with cCR-2 will be included in this analysis.
- Time to cCR-3 (TTcCR3) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first cCR-3. Only patients with cCR-3 will be included in this analysis.

- Time to objective response (TTOR) is defined as the time from the date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to the date of first objective response (CR_{MRD}-, CR, CRh, CRi, MLFS, or PR). Only patients with objective response will be included in this analysis.

The time (months) to response is generally calculated as (date of first occurrence of interested response category - date of first study drug administration from Cycle 1 + 1)/30.4375.

4.2.5. Event-free Survival

Event-free survival (EFS) is defined as the time from date of first study drug administration from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to treatment failure, relapse from CR (including CR_{MRD}-, CR, CRh and CRi), or death due to any cause, whichever occurs first. EFS analysis will take competitor Ivosidenib Phase III EFS definition and censoring rules as reference (Xu et al, 2020). Treatment failure is defined as failure to achieve CR (including CR_{MRD}-, CR, CRh and CRi) by Week 24. Subjects who do not achieve CR (including CR_{MRD}-, CR, CRh and CRi) by Week 24 will be considered to have had an event at Day 1 of first study drug administration from Cycle 1 (i.e. not from the date of single oral dose from the PK week for the dose escalation part). For the remaining CR responders (including CR_{MRD}-, CR, CRh and CRi), the event time will be the time of either disease relapse or death due to any cause, whichever occurs first. A response of CR (including CR_{MRD}-, CR, CRh and CRi) represents both disease control and establishment of hematopoiesis in subjects with AML and is an important predictor of OS (Dombret et al, 2015). Event-free survival will be censored upon initiation of a subsequent anticancer therapy.

The outcome (event or censor), type of event and the date of event or censoring to be considered for the EFS are presented in Table 4.

Table 4 Outcome and Event or Censoring Dates for EFS

Rule	Situation	Date of Event or Censoring	Outcome
1	CR by 24 weeks[a] then relapse between scheduled visit or after one missing tumor assessment visit	Date of relapse	Event (relapse)
2	CR by 24 weeks[a] then death (no relapse) between scheduled visit or after one missing tumor assessment visit	Date of death	Event (death)
3	On treatment ≥24 weeks without CR by 24 weeks[a]	Date of first administration of study treatment	Event (TF, on treatment ≥24 weeks without CR)
4	Treatment discontinuation prior to 24 weeks, without CR by 24 weeks[a]	Date of first administration of study treatment	Event (TF, treatment discontinuation prior to 24 weeks without CR)
5	On treatment <24 weeks without CR and active in study	Date of the last adequate disease assessment	Censored
6	CR by 24 weeks[a] then start subsequent anticancer therapy (prior to death or relapse or no relapse)	Date of the last adequate disease assessment documenting no relapse prior to start of subsequent anticancer therapy or missed response assessments	Censored
7	CR by 24 weeks[a] then death or relapse after missed or inadequate two or more consecutive tumor assessments		Censored
8	CR by 24 weeks[a] and neither relapse nor death		Censored
9	No baseline or post-baseline adequate disease assessment	Date of first administration of study treatment	Censored

CR: including CRMRD-, CR, CRh and CRi; EFS = event-free survival; TF = treatment failure.
[a] Based on the protocol schedule of assessments, "+1 week window" is allowed.
Note: The same algorithm for determination of one and two/more consecutive missing or inadequate assessments can be found in Section 4.2.3..

Reasons for censoring are included in Table 5 following the hierarchy.

Table 5 EFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No baseline or post-baseline adequate disease assessment	No baseline or post-baseline tumor assessments
2	On treatment <24 weeks without CR and active in study	On treatment <24 weeks, active in study
3	CR by 24 weeks then start subsequent anticancer therapy	CR by 24 weeks, start subsequent anticancer therapy
4	CR by 24 weeks then death or relapse after missed or inadequate two or more consecutive tumor assessments	CR by 24 weeks, missed or inadequate two or more consecutive tumor assessments
5	CR by 24 weeks, no relapse or death, lost to follow-up	CR by 24 weeks, lost to follow-up

6	CR by 24 weeks, no relapse or death, withdrawal by subject from the study	CR by 24 weeks, withdrawal by subject
7	CR by 24 weeks, no relapse or death, ongoing in study	CR by 24 weeks, ongoing without relapse or death

CR: including CRMRD-, CR, CRh and CRi; EFS = event-free survival.

4.2.6. Overall Survival

Overall Survival (OS) is defined as the time (months) from the start of study treatment from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) until the date of death due to any cause. OS is calculated as (date of death or last known alive – date of first administration of study treatment from Cycle 1 + 1)/30.4375.

In the rare case, if date of death is missing, date of death will be imputed using rules in Section 5.1.2.

Patients who do not die during the study will be censored at last known alive date. OS will not be censored at the date of initiating subsequent anticancer medication if a patient receives subsequent anticancer medication after discontinuation of the study drugs. Reasons for censoring are included in Table 6 following the hierarchy.

Table 6 OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and Withdrawal of consent in any disposition page or survival follow-up page	Withdrawal of consent
2	No event and lost to follow-up in any disposition page or survival follow-up page	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

OS=overall survival.

4.2.7. Progression-free Survival

Progression-free Survival (PFS) is defined as the time (months) from the start of study treatment from Cycle 1 in continuous cycle (i.e. not from the date of single oral dose from the PK week for the dose escalation part) to disease progression, or relapse, or death due to any cause, whichever occurs first. 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 (at least 2 cycles of study drug should be administered to determine PD) or relapse as defined by 2017 ELN criteria for AML patients, or

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

(iii) receiving subsequent anti-tumor therapy, whichever is earlier.

Patients without report of PD or death due to any cause at the time of analysis are censored as described in Table 7 below.

Table 7 Outcome and Event or Censoring Dates for PFS

Rule	Situation	Date of Progression or Censoring	Outcome

1	PD/relapse documented between schedule tumor assessment visit or after one missing tumor assessment visit	Date of first documented disease progression/relapse	Event
2	Death without PD/relapse between schedule tumor assessment visit or death on or before the second scheduled visit or death after one missing tumor assessment visit	Date of death	Event
3	No baseline or post-baseline tumor assessments available and subject dose not die	Date of first administration of study treatment	Censored
4	No death or PD/relapse by the time of data cut-off for final 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/relapse	Date of last adequate tumor assessment	Censored
6	Subsequent anti-tumor therapy started prior to PD/relapse or death	Date of last adequate assessment prior to or on date of initiation of subsequent therapy visit	Censored
7	PD/relapse or death after missed or inadequate two or more consecutive tumor assessment visits	Date of last adequate tumor assessment prior to missed visits or date of first administration of study treatment (if no post-baseline tumor assessment)	Censored

Note: An adequate tumor assessment is defined as an assessment where the Investigator determined response is CR_{MRD-}, CR, CRh, CRi, MLFS, PR, SD, and PD/relapse. If PD/relapse and subsequent anti-cancer therapy occur on the same day, will assume that the progression/relapse was documented first, e.g. outcome is progression/relapse and the date is the date of the assessment of progression/relapse.

Note: The same algorithm for determination of one and two/more consecutive missing or inadequate assessments can be found in Section 4.2.3.

PFS (months) is calculated as (date of event or censoring as per rules in Table 7 – date of first administration of study treatment from Cycle 1 + 1)/30.4375. Reasons for censoring are included in Table 8 following the hierarchy.

Table 8 PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No baseline or post-baseline tumor assessments available and subject dose not die	No baseline or post-baseline tumor assessments
2	Subsequent anti-tumor therapy started prior to PD/relapse or death	Subsequent anti-tumor therapy started prior to PD/relapse or death
4	PD/relapse or death after missed or inadequate two or more consecutive tumor assessment visits	Missed or inadequate two or more consecutive tumor assessment visits
5	Drops out before end of study, no progression /relapse or death, lost to follow-up	No death or PD/relapse, lost to follow-up
6	Drops out before end of study, no progression/relapse or death, withdrawal by subject from the study	No death or PD/relapse, withdrawal by subject
7	No death or PD/relapse by the time of data cut-off for the analysis	No death or PD/relapse by the time of data cut-off for the analysis

4.2.8. Transfusion Dependence

Baseline transfusion dependence (TD) is defined as receipt of any transfusions of red blood cells (RBCs) or platelets within 28 days prior to the first dose of stud drug administration. The baseline TD for RBCs is defined as receipt of any transfusions of RBCs within 28 days prior to the first dose of stud drug administration, and baseline TD for platelets is defined as receipt of any transfusions of platelets within 28 days prior to the first dose of stud drug administration.

Post-baseline transfusion independence (TI) is defined as the absence of RBC and platelet transfusions for a prespecified time during treatment period which is defined from the first dose of study drug administration from Cycle 1 in continuous cycle to 30 days after the last dose date or prior to the start of a subsequent anti-tumor therapy (whichever comes first). Two post-baseline TI overall and for its components will be derived based on the pre-specified time.

- Post-baseline TI-4 is defined to have no RBC or platelet transfusion for at least ≥4 weeks during treatment period.
- Post-baseline TI-8 is defined to have no RBC or platelet transfusion for at least ≥8 weeks during treatment period.
- Post-baseline TI-4 for RBC is defined to have no RBC transfusion for at least ≥4 weeks during treatment period.
- Post-baseline TI-8 for RBC is defined to have no RBC transfusion for at least ≥8 weeks during treatment period.
- Post-baseline TI-4 for platelet is defined to have no platelet transfusion for at least ≥4 weeks during treatment period.
- Post-baseline TI-8 for platelet is defined to have no platelet transfusion for at least ≥8 weeks during treatment period.

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 (months) = [Last non-zero dose date of study drug – first dose non-zero date of study drug (i.e. including single dose during the PK week) + 1] / 30.4375.

The actual duration of exposure (months) = [Cumulative days with non-zero study drug administered, and this includes the single dose during the PK week] / 30.4375.

Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 9.

Table 9 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	HMPL-306 [redacted] 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*30.4375)
Relative dose intensity (RDI) (%)	100 * [Dose intensity (mg/day) / ([redacted]) (mg/day)]
Percentage intended dose (PID) (%)	100 * [(actual duration of exposure) / (duration of exposure)]

§ Different doses (e.g. [redacted] mg PO QD, [redacted] mg PO QD, etc.) 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, echocardiogram (ECHO)/ multiple-gated acquisition (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).

4.4.1. 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.

4.4.2. 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 or higher. AEs will be collected from the time of signature of informed consent throughout the treatment period. AEs will be graded by investigator according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Missing severity grade will not be imputed, and will be summarized as 'Missing Grade' category in the by-grade analysis.

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 treatment-related AEs, AEs of special interest (AESI), 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. The AESI information will be identified programmingly by SMQ/PT.

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'.

4.4.3. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 10 will be measured.

Table 10 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC), platelet counts, Absolute Reticulocyte Count, Reticulocyte %, Absolute Neutrophil Count, Neutrophils %, Absolute Lymphocyte Count, Lymphocytes %, Absolute Monocyte Count, Monocytes %, Absolute Basophil Count, Basophils %, Absolute Eosinophil Count, Eosinophils%
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, direct bilirubin, indirect bilirubin, calcium, magnesium, chloride, creatinine, creatinine clearance rate, creatine phosphokinase, glucose, inorganic phosphorus, potassium, total protein, urine acid, glomerular filtration rate, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN)
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	evaluation of glucose, protein, RBC, WBC, Ketone body, Urobilinogen
Virology	HIV, HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), HCV (HCV antibody), cytomegalovirus (CMV) (CMV antibody), CMV DNA, HBV DNA, HCV RNA

Lab Category	Lab tests
Other tests	HbA1C, pregnancy test, and other non-protocol specified tests (if any)

Change from baseline in laboratory test results to each assessment will be calculated for selected parameters. 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 for selected parameters according to NCI CTCAE criteria, Version 5.0. 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 post baseline assessments.

- 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 increase <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 hematology, chemistry and coagulation 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.

4.4.4. 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 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 includes the following categories: Abnormal, clinically significant; Abnormal, not clinically significant; Normal; Unknown. For the ECG triplicate assessments at a timepoint, the worst interpretation will be applied for the summary.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 11.

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 11 Potentially Clinically Significant Criteria for ECG

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

4.4.5. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, heart rate, 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 time-point will be calculated.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 12.

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 also be calculated using these minimum and maximum values.

Table 12 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value
Systolic blood pressure (SBP) (mmHg)	≥160 ≥180 ≤90 ≥180 and an increase ≥20 from baseline
Diastolic blood pressure (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.

4.4.6. 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.

ECOG performance status is listed by patient and visit.

4.4.7. Echocardiogram (ECHO)

ECHOs are performed at Screening Period, on Day 1 of every treatment cycle for the first 3 cycles, every other cycle thereafter, and at EOT visit. Assessment parameters include left ventricular ejection fraction and overall interpretation of cardiac function. MUGAs are permitted if ECHOs cannot be performed.

4.4.8. 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 of the comprehensive physical examination as deemed appropriate by the investigator.

Results of physical examination are listed by patient and visit.

4.4.9. 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 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 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, safety and PK 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 SAS Enterprise® Version 8.3 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings.

Unless otherwise specified, analyses will be summarized:

- Efficacy analysis: by dose level for escalation stage (part 1) and by disease type for dose expansion (part 2).
- Analysis besides efficacy: by dose level and total for escalation stage (part 1) and by disease type and total for dose expansion (part 2).

In addition, main efficacy analysis will be repeated by IDH naïve/treated status (as defined in Section 5.2.4) and dose level for escalation stage (part 1) and by disease type for dose expansion (part 2).

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 treatment groups as defined in Table 13.

Table 13 Group Display in TLFs

Part of the study	Treatment Group	Treatment Description in Data Display
Part 1 - Dose Escalation	1	Cohort 1- CCI mg
	2	Cohort 2- CCI 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
Part 2 - Dose Expansion at HMPL-306 XX mg*	1	Cohort A: AML

*As only one patient at HMPL-306 CCI mg was enrolled in Part 2 Dose expansion Cohort A, this patient will be combined into Part 1 Dose escalation Cohort 8 CCI mg in all the summary tables and figures.

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. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%." 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. Other imputations are applied for calculations, if needed. 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 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. Last Known Alive Date

When a partial last known alive date is reported, below rules will be used:

- If only the day of the month is missing, then last known alive date will be imputed as 1st of the month;
- If both the day and the month are missing, then last known alive date will be imputed as 1st January of the year.

5.1.2.4. 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 last known alive date, then date of death will be replaced by last known alive date + 1 day。

If year is missing or both year and month are missing, then no imputation will be applied.

5.1.2.5. 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, 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.

5.1.2.6. 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.

5.1.2.7. 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, 15^{th} day will be imputed as the subsequent anti-tumor therapy date;

– If both the day and the month are missing, then July 1^{st} 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.

5.2. Analysis Methods

5.2.1. Patient Disposition

Summary of study disposition will be summarized by dose level and overall for Part 1 as well as by disease cohort and overall for Part 2:

Based on all subject set, the following will be summarized:

- Number of patients who signed the pre-screening informed consent
- Number of pre-screen failures and reason for pre-screen failures
- Number of patients who signed the informed consent
- Number of screen failures and reason for screen failure
- Number of patients enrolled
- Number of patients who do not receive study treatment
- Number of patients who received study treatment

Based on safety analysis set, the following will be summarized:

- Patients still on treatment
- Number and percentage of patients who discontinue the study drug
- Reason for study drug discontinuation (for study drug)
- 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 and follow-up status and inclusion in analysis sets will be also listed.

5.2.2. Protocol Deviations

Protocol deviations will be summarized descriptively (frequency and percentage) for patients with any major protocol deviation, and by major 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, baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2) calculated as baseline weight (kg)/ [baseline height (m)]^2, BMI category <18.5 kg/m^2, ≥18.5 and <24 kg/m^2, ≥24 kg/m^2), and baseline ECOG status, will be summarized and listed.

5.2.4. Disease Characteristics

Oncology history will be summarized descriptively on the safety analysis set for the following:

- Time since First Diagnosis of disease (months) = (date of first study treatment administration – date of first diagnosis of disease + 1)/30.4375

- IDH Mutation Status (local). It is derived based on the IDH mutation status collected on the CRF. That is, if the status of a patient contains "IDH1", "Arg132", "c.394C", the status for the patient will be assigned "IDH1"; if the status of a patient contains "IDH2", "Arg172", "Arg140", "c.419G", "c.515G", the status for the patient will be assigned "IDH2"; if the status of a patient contains any item for defining IDH1 and any item for defining IDH2, the status for the patient will be assigned "IDH1 and IDH2" indicating a dual mutation for the patient.
- IDH anti-cancer medication history (IDH pre-treated vs naïve): the status of receiving prior IDH anti-cancer medication is derived from the prior anti-cancer medications. That is, if a patient took any medication with the PT (upper case) or drug verbatim name (upper case) containing any of the terms "ENASIDENIB", "IVOSIDENIB", "OLUTASIDENIB" or "LY 3410738", the patient will be classified as "Pre-treated", otherwise, the category of "Naïve" will be assigned
- Oncology classification (AML, HR MDS, AITL)
- If AML:
    - AML type: if secondary AML, the related therapy
    - Time since initial AML diagnosis (months) = (date of first study treatment administration –initial date of AML diagnosis+ 1)/30.4375
    - AML Subtype by WHO 2016, and classification under each subtype (if applicable)
    - AML genetic risk stratification
- If MDS:
    - MDS type
    - Time since initial MDS diagnosis (months) = (date of first study treatment administration –initial date of MDS diagnosis+ 1)/30.4375
    - MDS Subtype by WHO 2016
    - IPSS-R Score Value and IPSS-R prognostic risk category
    - Cytogenetics Score
    - BM Blast %, Hemoglobin, Platelets, ANC
- If AITL:
    - AITL Subtype by WHO 2016
    - Time since initial AITL diagnosis (months) = (date of first study treatment administration –initial date of AITL diagnosis+ 1)/30.4375
    - Ann Arbor Staging at screening
    - B-symptoms present or not at screening
    - IPI Risk group
    - Have FDG-PET avid disease or not
    - Bone marrow involvement or not
- Anatomical location of Primary tumor

In addition, all disease characteristics and 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 or higher.

The number and percentage of patients with any past medical/surgical history within each SOC and PT will be provided on the safety analysis set. The analysis will be repeated for patients with on-going medical history.

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 separately for the safety analysis set.

Prior anti-cancer therapy overview

- Medication
  - Patients with at least one prior anti-cancer medication
  - Highest line of therapy (descriptive statistics)
  - Intent
  - Reason for treatment discontinuation
  - Best response for AML, MDS, AITL
  - Had disease progression or not

- Radiotherapy
  - Patients with at least one prior anti-cancer radiotherapy
  - Anatomical Site
  - Purpose

- Procedures / Surgeries
  - Patients with at least one prior anti-cancer procedures/surgeries
  - If this procedure is stem cell transplant, type of stem cell transplant

Subsequent anti-cancer therapy overview

- Medication: patients with at least one subsequent anti-cancer medication
- Radiotherapy: patients with at least one subsequent anti-cancer radiotherapy
- Procedures / Surgeries:
  - Patients with at least one subsequent anti-cancer procedures/surgeries
  - If this procedure is stem cell transplant, type of stem cell transplant

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.

In addition to the overview summary, prior and subsequent anti-cancer medications are coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e. ATC Level 2) and PT using the World Health Organization Drug Dictionary (WHO-DD) Version September 2024 or higher.

The prior anti-cancer medications will be summarized by presenting the number and percentage of patients by ATC and PT. 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 and PT within each ATC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer medications will be summarized by ATC and PT.

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.

In addition to the overview summary, 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.

In addition to the overview summary, 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 SOC and PT. Patients taking the same medication multiple times will only be counted once for that PT or SOC. Each summary will be ordered by descending order of incidence of SOC to total column and PT within each SOC. If the frequencies tie, an alphabetic order will be applied.

Similarly, the subsequent anti-cancer procedure or surgery will be summarized by SOC and PT.

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) are coded to Anatomical Therapeutic Classification (ATC) therapeutic group (i.e., ATC Level 2) and PT using the WHO-DD Version September 2024 or higher.

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 or the start of a subsequent anti-tumor therapy (whichever comes first) are denoted "Concomitant". Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be 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 on safety analysis set. 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 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 Procedures

Procedures or surgeries that occurs prior to the first dose of study treatment are denoted "Prior". Procedures or surgeries that occurs on or after first dose date but no later than 30 days after the last dose or the start of a subsequent anti-tumor therapy (whichever comes first) are denoted "Concomitant".

Prior and concomitant procedures or surgeries will be classified using the MedDRA version 27.1 or higher.

The prior and concomitant procedures or surgeries will be summarized by presenting the number and percentage of patients by PT and SOC on safety analysis set. Patients having the same procedure or surgeries 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 concomitant procedures or surgeries will be presented in listing.

5.2.9. Efficacy Analyses

All efficacy analyses will be based on the efficacy analysis set. The response evaluable analysis set will be used to conduct sensitivity analysis for tumor response.

No formal comparison or hypothesis testing is planned for this study. Two-sided 95% confidence intervals (CIs) will be calculated in the applicable summary, unless otherwise specified.

Main efficacy analysis will be repeated by IDH naïve and treated status based on efficacy analysis set.

All efficacy data will be listed.

5.2.9.1. BOR, Composite CRs, ORR, CBR

The relevant response endpoints are defined in Section 4.2.2. The number and percentage of patients in each category of derived BOR (CR, CR_{MRD-}, CRi, CRh, MLFS, PR, SD, PD and NE, with reasons being NE) will be summarized. The CR rate by 24 weeks, cCR-1 rate by 24 weeks, cCR-2 rate by 24 weeks, and cCR-3 rate by 24 weeks, ORR, and CBR will be summarized with the two-sided 95% exact confidence intervals (CIs) calculated using the Clopper-Pearson exact method.

The response evaluable analysis set will be used to conduct sensitivity analysis for the above tumor response endpoints.

Swimmer plot will be presented for the treatment duration and tumor responses, including length of treatment duration, timepoint response, death.

All tumor evaluation related data will be presented in listings.

5.2.9.2. DoCR/DoOR, EFS, PFS, and OS

For the time to event endpoints, such as various DoCRs/DoOR defined in Section 4.2.3, EFS and EFS for patients with CR by 24 weeks (if data allowed) defined in Section 4.2.5, OS defined in Section 4.2.6, and PFS defined in Section 4.2.7, the 25%, 50% (median), and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI which are calculated from a log-log transformation based on the method by Brookmeyer and Crowley (1982). For PFS and OS, additionally, estimates will be provided for the survival 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 and OS.

The duration of follow-up for PFS will be summarized by reversed Kaplan-Meier method (i.e. using different censoring rule which reverses censoring indicator of PFS, i.e. patients who progressed or died in PFS analysis will be censored at the date of progression or death, patients who are censored in PFS analysis will be assigned indicator of "event" with the same duration for PFS.) to calculate median, first and third quartiles and 95% CIs. The duration of follow-up for DoCR/DoOR, EFS, OS will be summarized similarly.

5.2.9.3. Time to response

For the various TTCRs/TTOR defined in Section 4.2.4, descriptive statistics will be provided.

5.2.9.4. Baseline Transfusion Dependence and Post-baseline Transfusion Independence

For the baseline TD and post-baseline TI defined in Section 4.2.8, the number and percentage of patients in each endpoint will be summarized descriptively. Clopper-Pearson exact method will be used to construct the two-sided 95% exact CIs.

In addition, shift tables between the baseline TD and post-baseline TI will be provided.

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, relative dose intensity category, and percentage intended dose for study drug) will be summarized on safety analysis set.

The following summary for dose modification will also be summarized.

- 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

Unless otherwise specified, the safety data based on safety analysis set 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 applies to parameters collected by visit) or prior to the start of a subsequent anti-tumor therapy (whichever comes first) after last dose.

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 based on the DLT evaluable analysis set.

DLTs will be listed.

5.2.11.2. Adverse Events

TEAE overview

An overall summary of TEAEs will include the number of patients with:

- 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

TEAE Summary

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

	Summary scope
TEAE	– Any TEAE – TEAEs with CTCAE grade 3 or higher (maximum CTCAE grade by Grade 5, Grade 4, Grade 3, Missing Grade) – TEAEs leading to dose modification o TEAEs leading to dose interruption o 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 5, Grade 4, Grade 3, Missing Grade) – Treatment-related TEAEs leading to dose modification o Treatment-related TEAEs leading to dose interruption o Treatment-related TEAEs leading to dose reduction

	Summary scope
	– 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 – Treatment-related serious 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, Missing Grade).

All TEAE and TEAE with CTCAE grade 3 or higher will also be summarized by SOC and PT.

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)
Differentiation syndrome	Differentiation syndrome (PT Code 10080638)

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

All AESIs will be summarized in frequency and percentage by AESI category, PT and maximum CTCAE grade (All Grade, Grade ≥3, Grade 1/2, Missing Grade). The followings overall safety summary 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).

Concomitant medication taken for hepatic function abnormal will be summarized by ATC and PT, and listed.

COVID-19 AE

COVID-19 AE will be identified by the following MedDRA Query (SMQ), and will be summarized (the number and percent of patients) by PT and maximum CTCAE grade (All Grade, Grade ⩾3, Grade 1/2, Missing Grade).

COVID-19	Search Strategy
COVID-19	COVID-19 (SMQ Code 20000237 Narrow search)

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 (1) all TEAEs of CTCAE Grade 3 or higher, (2) all treatment related AEs, (3) all SAEs, (4) all AEs leading to discontinuation of study drug, (5) all AEs leading to dose modification, (6) all AEs leading to death, (7) all AESIs, (8) COVID-19 AEs will be provided.

5.2.11.3. Death

Number of deaths and primary cause of death will be summarized descriptively. Similarly, the on-treatment deaths (i.e. deaths happening from first study drug administration to 30 days after the date of last administration of study drug or prior to the start of a subsequent anti-tumor therapy (whichever comes first)) and death during the follow-up period (i.e. deaths happening after 30 days after the date of last administration of study drug or prior to the start of a subsequent anti-tumor therapy (whichever comes first)) will also be tabulated.

All death information will be provided as patient list in which the on-treatment death will be flagged.

5.2.11.4. Laboratory Evaluations

For hematology, chemistry and coagulation labs, the observed values and change from baseline will be summarized by scheduled visit using descriptive statistics. For selected qualitative laboratory test (if any), 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, and 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 4.4.3 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 visits.

The criteria for potentially clinically significant findings are defined in Table 11. 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.

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

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 by scheduled visits using descriptive statistics during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 12) 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 scheduled visit and by maximum post-baseline score during the treatment period. 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

A by-patients listing of ECHO/MUGA values at each time point will be listed.

5.2.11.9. Differentiation Syndrome

Besides DS analysis as an AESI category described in Section 5.2.11.1, the following analysis will also be provided.

The number and percent of patients experiencing differentiation syndrome (DS) will be summarized. The number and percent of patients with following DS symptoms will be summarized:

- Dyspnea
- Unexplained fever
- Weight gain
- Unexplained Hypotension
- Acute renal failure
- Interstitial lung infiltration or pericardial effusion

In addition, the number and percent of patients with the Montesinos grading will also be summarized, the grading includes two grade level as moderate (2-3 symptoms) and severe (4 or more symptoms).

DS will be summarized by symptoms, Montesinos grade, and CTCAE grade.

Concomitant medication taken for DS will be summarized by ATC and PT, and listed.

A by-patients listing of differentiation syndrome will be listed.

5.2.11.10. Physical Examination, Ophthalmologic Examination

A listing of physical examination data, ophthalmologic examination data for all patients will be provided (where available).

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 and rearrangement for AML patients will be summarized, a patient with multiple gene mutation and rearrangement will be counted in each category. A listing of gene mutational data for all patients will be provided.

6. PLANNED ANALYSIS

6.1. 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.

6.2. Final Analysis

The final analysis will be conducted after final 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

- Added All Subject Set for pre-screening and screening summaries.
- Added Efficacy Analysis Set as primary analysis set for efficacy analysis and clarified definition of Response Evaluable Analysis Set as single dose from the PK week might not be an effective treatment. Safety Analysis Set was the primary set for safety analysis.
- 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 the 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.
- Removed DLT-equivalent analysis as investigator's evaluation of each AE satisfying DLT criteria or not was not well documented in EDC.
- Patients enrolled were summarized based on all subject set instead of safety analysis set.
- Removed Rate of CR+CRh, duration of CR+CRh and time to CR+CRh endpoints, since cCR-2 (rate of CRMRD-+CR+CRh) and cCR-3 (rate of CRMRD-+CR) are more meaningful.
- Removed Time to Hematologic Recurrence endpoint as it has the similar rationale for DOcCR1.
- Removed Disease Free Survival (DFS) endpoint as it has the same rationale for DOcCR1.

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