HUTCHMED

Clinical Study Protocol

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

Short Title	A Phase 1 Study of HMPL-306 in Advanced Hematological Malignancies With mIDH
Investigational Product(s):	HMPL-306
Protocol Number:	2020-306-GLOB1
Clinical Phase:	1
Issue Date:	02 November 2023
Amendment:	5
Sponsor:	HUTCHMED Limited 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
Regulatory Agency Identifier Number (s)	IND 150936 EudraCT 2020-003751-15

STATEMENT OF COMPLIANCE

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

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

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

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

SPONSOR'S APPROVAL

Title	A Phase 1, Open-Label, Multicenter Study of HMPL-306 in Advanced Hematological Malignancies With Isocitrate Dehydrogenase (IDH) Mutations
Protocol Number	2020-306-GLOB1
Amendment	5

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

Name: PPD , MD, PhD	**Title:** PPD HUTCHMED International Corporation
Signature: *See appended signature page.*	**Date:**[DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2020-306-GLOB1 and agree to the following:

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

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

DOCUMENT HISTORY

Amendment	**Issue Date**
Original Protocol	16 September 2020
1	20 October 2020
2	30 August 2021
3	15 October 2021
4	24 June 2022

AMENDMENT SUMMARY

This Protocol 2020-306-GLOB1 Amendment 5 (dated 02 November 2023) replaces Protocol 2020-306-GLOB1 Amendment 4 (dated 24 June 2022). This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

As of 23 October 2023, the dose escalation part of the current study has enrolled CCI patients with isocitrate dehydrogenase (IDH) mutations at increasing dose levels from CCI mg once daily (QD). CCI . The CCI mg QD dose is the highest tolerable dose evaluated in the dose escalation part. All the patients enrolled in the dose escalation part were relapsed or refractory acute myeloid leukemia (R/R AML) patients. The study did not enroll any patients with myelodysplastic syndrome (MDS) or angio-immunoblastic T-cell lymphoma (AITL), 2 other populations targeted for the originally planned expansion cohorts (Cohorts B and C) per Protocol 2020-306-GLOB1 Amendment 4.

Among the R/R AML patients, clinical responses were noted in patients who were naïve to prior IDH therapy at HMPL-306 doses of CCI mg QD or higher. CCI were noted in R/R AML patients who had CCI . However, all but CCI patients were enrolled in the lower dose cohorts (CCI mg QD) making it difficult to evaluate efficacy and safety of HMPL-306 in this subgroup of patients with a high unmet need for active subsequent therapy.

The primary purpose of Amendment 5 is to modify the dose expansion cohorts based upon the sponsor's strategic evaluation of the unmet need and the ability to enroll in selected populations.

In Expansion Cohort A, the study will enroll 10 R/R AML patients, limited to patients who have received prior IDH inhibitor therapy. The safety and tolerability as well as proof of activity will be evaluated at the highest tolerable dose level evaluated in the dose escalation part (CCI mg QD). If proof of activity is established at the higher dose level in this high-risk population, further evaluation at lower doses may be warranted in the future.

Expansion Cohorts B (MDS) and C (AITL) are removed, as these patients were not evaluated in the dose escalation part due to lack of enrollment in these populations. This change is not based on any concern for patient safety or efficacy relative to HMPL-306 treatment. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Details of changes made in prior amendments are summarized in Appendix 18.

Section Number	Summary of Change	Rationale for Change
Sponsor's Approval Page	Updated chief medical officer's name.	The administrative update was made to reflect the change in the sponsor's signatory.
Synopsis	Added study status as of Protocol Amendment 5 section.	The section was added to explain the study status and reason for the amendment.
Synopsis, Section 1.2 – Study Schematic, Section 4.1.2 –Part 2 (Dose Expansion), Section 5.2 –	Updated the target population for the dose expansion part to remove high-risk MDS and AITL cohorts and to specify that	Cohorts B and C were removed due to lack of enrollment. Cohort A was

Section Number	Summary of Change	Rationale for Change
Inclusion Criteria (Part 2, c), Section 9.2.7 – Efficacy Analysis	patients must not have standard therapeutic options available and must have received at least 1 prior line of therapy with IDH inhibitors.	modified based upon the sponsor's strategic evaluation of the unmet need.
Synopsis, Section 3 –Objectives and Endpoints (Table 3, Objective and Corresponding Endpoints), Section 4.2.3 – Rationale for Biomarker Testing, Section 6.1.15.1 – Sample Collection and Handling, Section 6.1.15.2 – Analytical Procedures, Section 9.1.3 – Analysis Sets, Section 9.2.6 – Pharmacodynamic Analysis, Appendix 2 – PK/PD/Biomarker/ECG Assessments for Expansion Cohorts	Removed collection of bone marrow samples for concentrations of 2-hydroxyglutarichdrocyglutaric acid (2-HG)	Language removed to simplify biological sample collection.
Synopsis, Section 9.1.2 – Sample Size Rationale	Updated total number of patients to 40 to 50 patients (from 75 patients).	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Synopsis, Section 1.2 – Study Schematic, Section 4.1.2 – Part 2 (Dose Expansion), Section 6.2.2.2 – Stopping Rules for a Cohort or the Study (Dose Expansion Part), and CCI [redacted], Section 9.1.2 – Sample Size Rationale, Section 9.1.2.2 –Dose Expansion Part	Updated number of patients and/or number of cohorts, if applicable, for Part 2 to approximately 10 patients (from approximately 15 patients per cohort or 45 patients total).	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Section 1.2 – Study Schematic	Updated to remove Cohorts B and C and modify Cohort A.	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Section 1.3 – Schedule of Events, (Table 1, Schedule of Events [Dose Escalation] and Table 2, Schedule of Events [Dose Expansion – Relapsed/Refractory Acute Myeloid Leukemia])	Revised "Bone marrow aspiration and/or biopsy" to "Blood and/or bone marrow aspiration and/or biopsy." Revised footnote o (Table 1) and footnote n (Table 2) to "Whole blood and/or bone marrow samples will be collected and provided to a central laboratory for CCI [redacted] analyses." Added footnote y to state that, "Bone marrow aspiration or biopsy will include local immunophenotyping, cytogenetic analysis, and molecular genetic testing. Additional procedural details are available in Section 6.1.10.3, Section 6.1.10.13, and Appendix 17." Footnote y symbol was added to "Tumor evaluation/imaging."	Revisions made to clarify biological sample collection and testing requirements.

Section Number	Summary of Change	Rationale for Change
Section 1.3 – Schedule of Events, Table 2 – Schedule of Events (Dose Expansion – Relapsed/Refractory Acute Myeloid Leukemia)	Revised table title to add, "Relapsed/Refractory Acute Myeloid Leukemia." Added "Minimal residual disease evaluation" with timing to match "Tumor evaluation/imaging." Removed "Ann-Arbor staging" and associated footnote v. Subsequent footnote was relettered v.	Table title revision was made for clarity. Evaluation was added to allow for proof-of-concept evaluation of relevance of minimal residual disease. Ann-Arbor staging removed because of the removal of AITL cohort.
Section 2.1.2.2 – Mutations and Malignancies, Section 2.3.1 – Benefit-Risk Assessment	Added a statement that patients who fail IDH inhibitor therapies do not have any standard treatment options available.	Revision provides justification for modification of patient population for Part 2.
Section 2.2 – Background	Added language consistent with the "Study status as of Protocol Amendment 5" section of the synopsis and the Amendment Summary	Language was added to explain the study status and reason for the amendment.
Section 2.3.1 – Benefit-Risk Assessment	Added the statement, "Additionally, AML patients who fail IDH therapies do not have any standard treatment options available, making them a population with very high unmet need (NCCN-AML 2021)." Added the statement, "The incidence rate and severity of toxicities in these FDA approved IDH1 and IDH2 inhibitors is consistent with the safety profile of HMPL-306 in patients with hematologic malignancies. Further details on identified and potential risks of HMPL-306 are provided in the Investigator's Brochure (IB)." Revised the following statement, "In summary, patients with AML who have received at least 2 prior lines of therapy **including IDH inhibitors** and patients with AITL and HR-MDS who have received at least 1 prior line of therapy do not have viable treatment options."	Language added to provide clarity for the information to support benefit:risk and aligned to established therapies.
Section 4.1.1 –Part 1 (Dose Escalation), Safety Review Committee, Section 11.1.1 – Safety Review Committee	Added statement "The SRC, on an ongoing basis, will also monitor the benefit-risk of HMPL-306 treatment in the expansion cohort and make recommendations on the continuation of enrollment in the study."	Revision provides added safety monitoring measures for Part 2.
Section 4.1.2 – Part 2 (Dose Expansion), Study Treatment, Section 7.1.2 – Dose Expansion	Revised to indicate that patients will receive HMPL-306 daily at "CCI mg QD (highest tolerable dose evaluated in the dose escalation part."	Revisions reflect the highest tolerable dose from Part 1.

Section Number	Summary of Change	Rationale for Change
Section 4.2.2.1 – Relapsed/Refractory Acute Myeloid Leukemia, Section 4.2.2.2 – Relapsed/Refractory High-Risk Myelodysplastic Syndrome, Section 4.2.2.3 – Relapsed or Refractory Angio-immunoblastic T-cell Lymphoma	Removed "Cohort A," "Cohort B," and "Cohort C" designations, respectively.	All the patients enrolled in the dose escalation part were R/R AML patients. The study did not enroll any patients with myelodysplastic syndrome MDS or AITL, 2 other populations targeted for the originally planned expansion cohorts (Cohorts B and C) per Protocol 2020-306-GLOB1 Amendment 4.
Section 4.2.3 – Rationale for Biomarker Testing	Removed possible concomitant co-mutation sample analysis and added instead that results of local IDH mutation testing at screening will be used for further analyses.	Language removed for clarification.
Section 5.2 – Inclusion Criteria (Part 2)	Removed c, "Patients with HR-MDS must have an IPSS-R score of >4.5 (high and very high risk) Combined d and e to specify that patients will have R/R AML, no standard therapeutic options available, and must have progressed on prior IDH treatment. Removed patients with HR-MDS and AITL. Removed Inclusion Criterion #5 and 6 (AITL patients).	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Section 5.3 – Exclusion Criteria	Added Exclusion Criterion #20 for Part 2 only.	Addition specifies the time period between treatment with IDH inhibitor and study drug administration.
Section 6.1.2 – PK Week	Added statement that PK week for a particular dose cohort will be optional and not mandatory if PK week data from 5 patients have been collected at the same dose.	Language added to clarify the requirement of PK week.
Section 7.6.1 – Differentiation Syndrome Handling Principles	Removed statements that there are no clear diagnostic criteria for differentiation syndrome and the associated clinical symptoms.	New language was added to replace the statements that were removed in order to provide further clarification on clinical diagnosis of DS (Differentiation Syndrome)
Section 8.2.2 – Expedited Reporting	Added "Hy's Law" to list of events that must be reported by investigators to the sponsor within 24 hours of first learning of the event.	Revision was made for the importance of ensuring prompt reporting of Hy's law/DILI cases following guidance from the Health Authorities (FDA Guidance

Section Number	Summary of Change	Rationale for Change
		2009) https://www.fda.gov/media/116737/download
Section 8.7 – Duration of Follow-up for Adverse Events	Added, "start of new oncology treatment" as an end point for follow-up of AEs and SAEs.	Revision made to provide further clarification on the end period of safety follow up
Section 9.1.2.2 – Dose Expansion Part	Updated the probability of observing an AE or CR in Dose Expansion Part given the change in sample size.	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Section 9.2.1 – Patient Disposition, Section 9.2.3 – Prior and Concomitant Medications	Updated summarization to be by overall and by "cohorts" (not tumor types).	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A.
Section 9.2.7 – Efficacy Analysis	Added a statement that the efficacy analysis will only be conducted for AML patients. Other tumor assessment data (HR-MDS or AITL) will be listed. Revised baseline transfusion dependence timing to 28 days (from 56 days). Removed efficacy data language regarding corresponding tumor types from Part 1.	The updates were made to reflect the removal of Cohorts B and C, and modification of Cohort A and to reflect the response to FDA Information Request received on 20 September 2022 for IND 150936.
Section 9.2.7.2 –Tumor Response Endpoints for Patients with HR-MDS, Section 9.2.7.3 –Tumor Response Endpoints for Patients with AITL	Sections deleted.	The deletions were made to reflect the removal of Cohorts B and C.
Appendix 1 – PK/PD/Biomarker/ECG Assessments for Escalation Cohorts	Blood and Bone Marrow Samples for Gene Mutation Analysis – all sample collections removed except for screening.	Revisions made to simplify biological sample collection and testing schedule.
Appendix 2 – PK/PD/Biomarker/ECG Assessments for Expansion Cohort	Added an X for blood sample collection for 2-HG at predose on C1D1. Removed X for blood sample collection for 2-HG at predose on C1D2 and C2D2. Shifted the study day for serial PK blood sample collection from C2D1 to C3D1. Shifted the study day for predose PK blood sample collection from C2D2 to C3D2. Shifted the study day for triplicate ECG collection from C2D1 to C3D1 Removed footnote 4.	Revisions made to optimize biological sample and ECG collection schedule.

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LIST OF ABBREVIATIONS

Abbreviations	Definitions
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
2-HG	2-hydroxyglutaric acid
ADL	Activities of daily living
AE	Adverse event
AITL	Angio-immunoblastic T-cell lymphoma
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AR	Accumulation ratio
AST	Aspartate aminotransferase
$AUC_{0\text{-}24}$	Area under the plasma concentration-time curve from time 0 to 24 hours
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time 0 to time of the last measurable concentration
$AUC_{0\text{-}\tau}$	Area under the plasma concentration-time curve within the dosing interval
BCRP	Breast cancer resistance protein
BID	Twice daily
C1D1	Cycle 1 Day 1
CBR	Clinical benefit rate
CI	Confidence interval
CIR	Cumulative incidence of relapse
CL/F	Total plasma clearance of drug after extravascular administration
C_{max}	Maximum observed plasma concentration
C_{maxss}	Maximum observed plasma concentration (at steady state)
C_{min}	Minimum plasma concentration
C_{minss}	Minimum observed plasma concentration (at steady state)
CMR	Complete metabolic response
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form (electronic or paper)
CRh	Complete response with partial hematological recovery
CRi	Complete response with incomplete count recovery
$CR_{MRD\text{-}}$	Complete response with negative minimal residual disease
CRO	Contract research organization

Abbreviations	Definitions
CRR	Complete radiologic response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
CYP	Cytochrome p450
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DS	Differentiation syndrome
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EFS	Event-free survival
EOT	End of treatment
ESMO	European Society for Medical Oncology
EUA	Emergency use authorization
FIH	First-in-human
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HI	Hematological improvement
HIV	Human immunodeficiency virus
HMA	hypomethylating agent(s)
HNSTD	Highest nonseverely toxic dose
HR-MDS	High-risk myelodysplastic syndrome
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDH	Isocitrate dehydrogenase

Abbreviations	Definitions
IEC	Independent Ethics Committee
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
IWG	International working group
MATE	Multidrug and toxin extrusion
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mIDH	Mutant IDH
MLFS	Morphologically leukemia-free state
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval-2
MUGA	Multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequence
NOAEL	No-observed-adverse-effect level
OATP	Organic anion transporting polypeptide
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Pharmacodynamic(s)
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PrD	Progressive disease
P-gp	P-glycoproteins
PK	Pharmacokinetic(s)
PMR	Partial metabolic response
PO	Orally
PR	Partial response
PRe	Partial remission
PS	Performance status
PT	Prothrombin time
QD	Once daily
QTc	Corrected QT

Abbreviations	Definitions
QTcF	QT interval corrected for heart rate using Fridericia's formula
R/R	Relapsed/refractory
RBC	Red blood cell
RP2D	Recommended phase 2 dose
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
SRC	Safety Review Committee
$t_{1/2}$	Elimination half-life
TE	Target engagement
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
T_{max}	Time to reach the maximum plasma concentration
TTR	Time to response
CCI	[redacted]
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution
WBC	White blood cell
α-KG	α-Ketoglutaric acid
λ_z	Apparent first-order rate constant associated with the terminal portion of the curve

1 PROTOCOL SUMMARY

1.1 Synopsis

Title	A Phase 1, Open-Label, Multicenter Study of HMPL-306 in Advanced Hematological Malignancies With Isocitrate Dehydrogenase (IDH) Mutations
Short Title	A Phase 1 Study of HMPL-306 in Advanced Hematological Malignancies With mIDH
Phase	1
Study Status as of Protocol Amendment 5	As of 23 October 2023, the dose expansion cohorts of Study 2020-306-GLOB1 will be modified based upon the strategic evaluation of the unmet need and the ability to enroll in selected populations. In Expansion Cohort A, the study will enroll 10 relapsed or refractory acute myeloid leukemia (R/R AML) patients, limited to patients who have received prior IDH inhibitor therapy. The safety and tolerability as well as proof of activity will be evaluated at the highest tolerable dose level evaluated in the dose escalation part (CCI mg once daily [QD]). Expansion Cohorts B (myelodysplastic syndrome [MDS]) and C (angio-immnoblastic T-cell lymphoma [AITL]) are removed, as these patients were not evaluated in the dose escalation part due to lack of enrollment in these populations. This change is not based on any concern for patient safety or efficacy relative to HMPL-306 treatment.
Rationale	Isocitrate dehydrogenase is the enzyme that catalyzes 1 of 4 rate-limiting steps in the Krebs cycle, or citric acid cycle. IDH mutation plays a major role in carcinogenesis and has been found in multiple tumors, including hematological malignancies, such as AML, high-risk myelodysplastic syndrome (HR-MDS), myeloproliferative neoplasm (MPN), and AITL, and solid tumors such as glioma, chondrosarcoma, and cholangiocarcinoma. Clinical development of an inhibitor such as HMPL-306 that targets, inhibits, and suppresses multiple mutant IDHs (mIDHs) concurrently could lead to significant and durable clinical benefit.
Target Population	Adult male and female patients ≥18 years of age with advanced relapsed, refractory, or resistant hematological malignancies that harbor IDH mutations (or co-mutation). Dose expansion part will enroll R/R AML patients who must not have standard therapeutic options available. The patients must have received at least 1 prior line of therapy with IDH inhibitors.
Intervention	Part 1 (Dose escalation): CCI mg HMPL-306 orally (PO) once daily (QD) Part 2 (Dose expansion): Recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD) from Part 1 PO QD
Description of Sites	Approximately 40 study sites in the United States, Europe, Australia, and Asia.

Objectives and Endpoints

Objectives	**Corresponding Endpoints**
Primary: • Part 1: To evaluate the safety and tolerability of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	**Primary:** • MTD and/or 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: 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	**Secondary:** • Best overall response, 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-hydroxyglutarichydroxyglutaric acid (2-HG)
Exploratory: • To explore relationships between changes in frequency of genetic mutations, efficacy, PK, PD, and safety after HMPL-306 treatment	**Exploratory:** • 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	

Brief Summary:

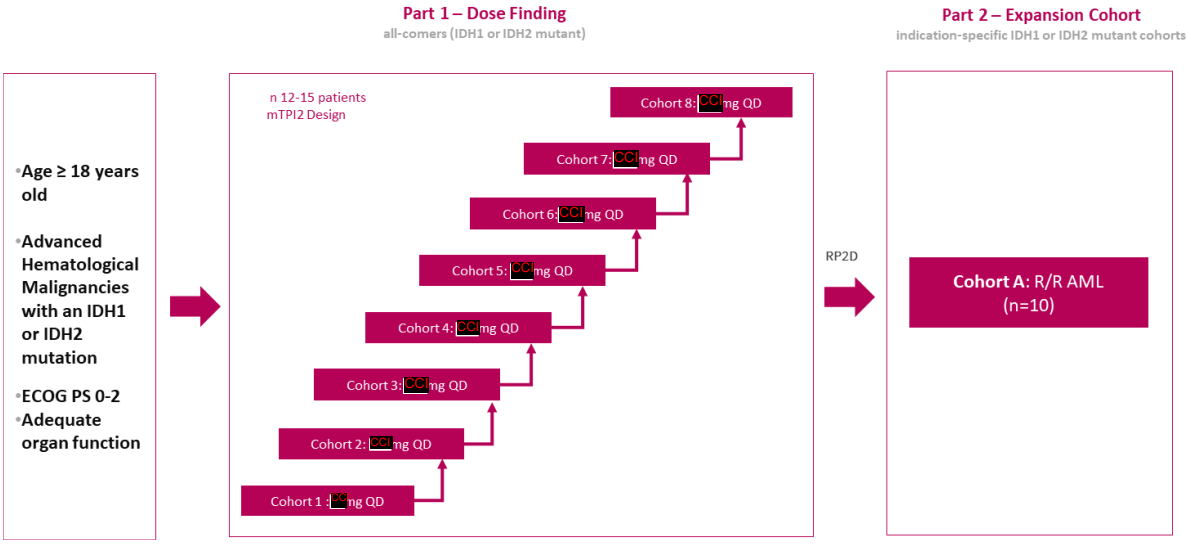
This is a phase 1, open-label, multicenter, single-arm study to evaluate safety, tolerability, PK, PD, and preliminary efficacy of HMPL-306 administered orally in treatment of patients with advanced relapsed, refractory, or resistant hematological malignancies that harbor IDH mutations (or co-mutations). The study consists of 2 parts: a dose escalation part (Part 1) and a dose expansion part (Part 2). The dose escalation part will determine the MTD/R2PD. The dose expansion part will administer the MTD/RP2D to:

- R/R AML patients who do not have standard therapeutic options available. The patients must have received at least 1 prior line of therapy with IDH inhibitors

Condition/Disease	Advanced relapsed, refractory, or resistant hematological malignancies that harbor IDH mutations
Study Duration	Approximately 36 months
Treatment Duration	28-day continuous dosing treatment cycle
Health Measurement/Observation	This study will determine the MTD and/or RP2D as well as safety assessments including DLTs, TEAEs, SAEs, ECGs, and clinical laboratory abnormalities. During the dose expansion part, patients will receive HMPL-306 daily at MTD/RP2D, for treatment cycles of 28 days until disease progression, death, intolerable toxicity, withdrawal of consent, lost to follow-up, conditions are met per Section 6.2.1, or end of study, whichever comes first.
Visit Frequency	PK week: every day for 1 week (Part 1 only) Cycle 1: every week (±1 day, except D1)

	Cycle 2: every 2 weeks (±1 day) Cycle 3 and onwards: day 1 (±3 days) Treatment completion: within 7 days (±3 days) after the last dose
Number of Patients	A total of approximately 40 to 50 evaluable patients expected between Parts 1 and 2. Part 1: at least 3 patients will be enrolled at each dose level; approximately 24 to 30 evaluable patients Part 2: approximately 10 patients
Intervention Groups and Duration	Part 1: CCI [redacted] mg of HMPL-306 PO QD administered to groups of at least 3 patients for 28-day cycles Part 2: MTD/RP2D as determined in Part 1, administered PO QD to approximately 10 patients for 28-day cycles
Data Monitoring/Other Committee	Yes

1.2 Study Schematic



AML=acute myeloid leukemia; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IDH=isocitrate dehydrogenase; mTPI2=modified toxicity probability interval-2; QD=once daily; RP2D = recommended phase 2 dose R/R = relapsed/refractory.

Note: Patients in dose expansion must have documented IDH1 or IDH2 mutations. Patients must not have any standard therapeutic options available and must have received at least 1 prior line of therapy with IDH inhibitors.

1.3 Schedule of Events

The Schedules of Events are presented in Table 1 (dose escalation) and Table 2 (dose expansion).

Table 1 Schedule of Events (Dose Escalation)

Cycle/Period	**Pre-screening**	**Screening**	**PK Week[a]**	**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit			**Single Dose Visit**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 days after last dose**	**30 days after EOT Visit**	**Every 12 weeks from EOT Visit**	**Every 12 weeks from EOT Visit**
Visit window (days)		**-28 to -1**	**0**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities														
Pre-screening informed consent	X													
Main informed consent[b]		X												
mIDH status[c]		X												
Medical history and demographics[d]	X	X												
Prior and concomitant medications and concomitant procedures[e]		X	X	X	X	X	X	X	X	X	X	X	X	
Height[f]		X												
Physical examination, vital signs, and weight[f]		X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status[f]		X	X	X		X		X	X	X	X	X		
Ophthalmologic examination[g]		X						X (±1 week)		Every 12 weeks from C4D1 (±7 days)		X		
Laboratory evaluations:[f]														
Hematology[h]		X	X	X	X	X	X	X	X	X	X	X		
Blood chemistry[i]		X	X		X	X	X	X	X	X	X	X		
Blood amylase and lipase			X		X	X	X	X	X	X	X	X		
Fasting lipid panel[j]			X					X		X	X	X		
Coagulation indicators[k]			X				X	X	X	X		X		
HbA1C			X					X		X	X	X		
Pregnancy test[l]		X	X	X				X		X	X	X		

Cycle/Period	**Pre-screening**	**Screening**	**PK Week[a]**	**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit			**Single Dose Visit**	**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 days after last dose**	**30 days after EOT Visit**	**Every 12 weeks from EOT Visit**	**Every 12 weeks from EOT Visit**
Visit window (days)		**-28 to -1**	**0**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities														
Urinalysis[m]			X					X		X				
Virological screening[n]		X												
Blood and/or bone marrow aspiration and/or biopsy[o]			Refer to Appendix 1											
PK and PD assessments			Refer to Appendix 1											
12-lead ECG[p]			Refer to Appendix 1											
ECHO/MUGA scan[q]		X		X				X		Cycle 3 Day 1 then Day 1 of every odd cycle	X			
Tumor evaluation/imaging[y]		X		Every 8 weeks (±7 days) during the first 24 weeks and every 12 weeks (±14 days) thereafter							X		X	
Blood transfusion history[r]		X												
Blood transfusion record[s]			X	X	X	X	X	X	X	X	X	X		
Drug/dispense/return[v]			X	X				X		X				
Study drug administration			Refer to Table 4											
AEs[t]	X	X	X	X	X	X	X	X	X	X	X	X		
Survival follow-up[u]														X
Ann-Arbor staging[w]		X												
Risk stratification/Prognostic scoring[x]		X												

2-HG=2-hydroxyglutaric acid; AE=adverse event; AITL=angio-immunoblastic T-cell lymphoma; aPTT=activated partial thromboplastin time; C=cycle; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HbA1C=hemoglobin A1C; ICF=informed consent form; IDH=isocitrate dehydrogenase; INR=international normalized ratio; IPI=international prognostic index; IPSS-R Score=Revised International Prognostic Scoring System; HR-MDS=high-risk myelodysplastic syndrome; mIDH=mutant IDH; MUGA=multigated acquisition; OCT=optical coherence tomography; PD=pharmacodynamics; PK=pharmacokinetics; PR=partial response; PT=prothrombin time.

[a] PK week is applicable to the dose escalation cohorts only. See Appendix 1 for details. For patients enrolled in dose escalation, a single dose of HMPL-306 will be administered on D1 of the PK week (7 days prior to C1D1) for each dose level, and serial blood samples will be collected (for analysis of plasma concentrations of HMPL-306, 2-HG, and other biological markers as defined by the sponsor) and ECG as specified in Appendix 1.

[b] Procedural details are available in Section 5.1.1.

[c] Patients should have a local report of IDH mutational analysis, confirming mIDH.

[d] Procedural details for medical history and demographics are available in Section 6.1.3.

[e] Procedural details for prior and concomitant medications/treatments are available in Section 6.1.4.

[f] Procedural details are available in Section 6.1.6 (vital signs), Section 6.1.7 (physical examination, weight, and height), Section 6.1.8 (ECOG performance status), and Section 6.1.10 (laboratory evaluations).

[g] Ophthalmologic assessments, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, OCT, and intraocular pressure will be performed during the Screening Period. If the subject has undergone the relevant examinations 60 days before the start of study treatment (C1D1), they need not be repeated. After the start of study drug administration, OCT will be performed at 6 weeks (±1 week), then OCT, eye appearance, and slit lamp examinations will be performed every 12 weeks (±1 week) from C4D1 and at the EOT visit. Other ophthalmological 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

[h] Procedural details for hematology are available in Section 6.1.10.1.

[i] Procedural details for blood chemistry are available in Section 6.1.10.4.

[j] Procedural details for fasting lipid panel are available in Section 6.1.10.6.

[k] Coagulation tests include PT, INR, and aPTT. Additional procedural details for coagulation indicators are available in Section 6.1.10.7.

[l] Additional procedural details for pregnancy testing are available in Section 6.1.10.9.

[m] Urinalysis includes urine glucose, protein, ketone body, red blood cells, white blood cells, and urobilinogen. Additional procedural details are available in Section 6.1.10.10.

[n] Additional procedural details for virological screening are available in Section 6.1.10.11.

[o] Whole blood and/or bone marrow samples will be collected and provided to a central laboratory for CCI [redacted] analyses. See Appendix 1 for details.

[p] Evaluation time points are shown in Appendix 1 and Appendix 2. Additional procedural details for the 12-lead ECG are available in Section 6.1.11.

[q] Additional procedural details are provided for ECHO and MUGA in Section 6.1.12.

[r] Additional procedural details for blood transfusion history are provided in Section 6.1.10.2.

[s] Additional procedural details for blood transfusion record are provided in Section 6.1.10.2.

[t] AEs due to the protocol-required intervention will be collected from signature of the ICF. Additional details are provided in Section 5.1.1.

[u] Survival follow-up should be performed every 12 weeks (±2 weeks) after the EOT Visit. Additional details are provided in Section 6.1.19.

[v] If tumor evaluation shows progressive disease during previous cycle and new drug has been dispensed, patient must return all unused study drug on 30-day safety visit after EOT.

[w] Applicable for patients with AITL; see Appendix 13 for a description of Ann-Arbor staging.

[x] Additional procedural details for risk stratification/prognostic stratification and scoring are available in Section 6.1.14.1.
[y] Bone marrow aspiration or biopsy will include local immunophenotyping, cytogenetic analysis, and molecular genetic testing. Additional procedural details are available in Section 6.1.10.3, Section 6.1.10.13, and Appendix 17.

Table 2 Schedule of Events (Dose Expansion - Relapsed/Refractory Acute Myeloid Leukemia)

Cycle/Period	**Pre-screening**	**Screening**		**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit				**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 days after last dose**	**30 days after EOT Visit**	**Every 12 weeks from EOT Visit**	**Every 12 weeks from EOT Visit**
Visit window (days)		**-28 to -1**	**-7 to -1**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities														
Pre-screening informed consent	X													
Main informed consent[a]		X												
mIDH status[b]		X												
Medical history and demographics[c]	X	X												
Prior and concomitant medications and concomitant procedures[d]		X		X	X	X	X	X	X	X	X	X	X	
Height[e]		X												
Physical examination, vital signs, and weight[e]		X		X	X	X	X	X	X	X	X	X		
ECOG performance status[e]		X		X		X		X	X	X	X	X		
Ophthalmologic examination[f]		X						X (±1 week)		Every 12 weeks from C4D1 (±7 days)				
Laboratory evaluations:[e]														
Hematology[g]			X		X	X	X	X	X	X	X	X		
Blood chemistry[h]			X		X	X	X	X	X	X	X	X		
Blood amylase and lipase			X		X	X	X	X	X	X	X	X		

Cycle/Period	**Pre-screening**	**Screening**		**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit				**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 days after last dose**	**30 days after EOT Visit**	**Every 12 weeks from EOT Visit**	**Every 12 weeks from EOT Visit**
Visit window (days)		**-28 to -1**	**-7 to -1**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities														
Fasting lipid panel[i]			X					X		X	X	X		
Coagulation indicators[j]			X				X	X	X	X		X		
HbA1C			X					X		X	X	X		
Pregnancy test[k]		X	X	X				X		X	X	X		
Urinalysis[l]			X					X		X				
Virological screening[m]		X												
Bone marrow aspiration and/or biopsy[n]				Refer to Appendix 2										
PK and PD assessments				Refer to Appendix 2										
12-lead ECG [o]				Refer to Appendix 2										
ECHO/MUGA scan[p]		X		X				X		Cycle 3 Day 1 and every odd cycle thereafter	X			
Tumor evaluation/imaging		X		Every 8 weeks (±7 days) during the first 24 weeks and every 12 weeks (±14 days) thereafter							X		X	
Minimal residual disease evaluation		X		Every 8 weeks (±7 days) during the first 24 weeks and every 12 weeks (±14 days) thereafter							X		X	
Blood transfusion history[q]		X										X		
Blood transfusion record[r]			X	X	X	X	X	X	X	X	X			
Drug/dispense/return[u]				X				X		X				

Cycle/Period	**Pre-screening**	**Screening**		**C1**				**C2**		**C3+**	**EOT**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Visit				**D1**	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**Within 7 days after last dose**	**30 days after EOT Visit**	**Every 12 weeks from EOT Visit**	**Every 12 weeks from EOT Visit**
Visit window (days)		**-28 to -1**	**-7 to -1**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±14**
Activities														
Study drug administration				Refer to Table 4										
AEs[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Follow-up[t]														X
-														
Risk stratification/Prognostic scoring[v]		X												

AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; D=day; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; HbA1C=hemoglobin A1C; ICF=informed consent form; IDH=isocitrate dehydrogenase; INR=international normalized ratio; mIDH=mutant IDH; MUGA=multigated acquisition; OCT=optical coherence tomography; PD=pharmacodynamics; PK=pharmacokinetics; PR=partial response; PT=prothrombin time.

[a] Procedural details are available in Section 5.1.1.

[b] Patients should have a local report of IDH mutational analysis, confirming mIDH.

[c] Procedural details for medical history and demographics are available in Section 6.1.3.

[d] Procedural details for prior and concomitant medications/treatments are available in Section 6.1.4.

[e] Procedural details are available in Section 6.1.6 (vital signs), Section 6.1.7 (physical examination, weight, and height), Section 6.1.8 (ECOG performance status), and Section 6.1.10 (laboratory evaluations).

[f] Ophthalmologic assessments, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, OCT, and intraocular pressure will be performed during the Screening Period. If the subject has undergone the relevant examinations 60 days before the start of study treatment (C1D1), they need not be repeated. After the start of study drug administration, OCT will be performed at 6 weeks (±1 week), then OCT, eye appearance, and slit lamp examinations will be performed every 12 weeks (±1 week) from C4D1 and at the EOT visit. Other ophthalmologic 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

[g] Procedural details for hematology are available in Section 6.1.10.1.

[h] Procedural details for blood chemistry are available in Section 6.1.10.4.

[i] Procedural details for fasting lipid panel are available in Section 6.1.10.6.

[j] Coagulation tests include PT, INR, and aPTT. Additional procedural details for coagulation indicators are available in Section 6.1.10.7.

[k] Additional procedural details for pregnancy testing are available in Section 6.1.10.9.

[l] Urinalysis includes urine glucose, protein, ketone body, red blood cells, white blood cells, and urobilinogen. Additional procedural details are available in Section 6.1.10.10.
[m] Additional procedural details for virological screening are available in Section 6.1.10.11.
[n] Whole blood and/or bone marrow samples will be collected and provided to a central laboratory for CCI analyses. See Appendix 1 for details.
[o] Evaluation time points are shown in Appendix 2. Additional procedural details for the 12-lead ECG are available in Section 6.1.11.
[p] Additional procedural details are provided for ECHO and MUGA in Section 6.1.12.
[q] Additional procedural details for blood transfusion history are provided in Section 6.1.10.2.
[r] Additional procedural details for blood transfusion record are provided in Section 6.1.10.2.
[s] AEs due to the protocol-required intervention will be collected from signature of the ICF. Additional details are provided in Section 5.1.1.
[t] Survival follow-up should be performed every 12 weeks (±2 weeks) after the EOT Visit. Additional details are provided in Section 6.1.19.
[u] If tumor evaluation shows progressive disease during previous cycle and new drug has been dispensed, patient must return all unused study drug on 30-day safety visit after EOT.
[v] Additional procedural details for risk stratification/prognostic stratification and scoring are available in Section 6.1.14.1.

2 INTRODUCTION

2.1 Study Rationale

2.1.1 Investigational Product

HMPL-306 is an innovative, small-molecule, orally available, highly selective, and potent inhibitor of IDH1 and IDH2 mutations.

2.1.2 Isocitrate Dehydrogenase

Isocitrate dehydrogenase (IDH) is the enzyme that catalyzes 1 of 4 rate-limiting steps in tricarboxylic acid cycle. Tricarboxylic acid cycle, also called Krebs cycle and/or citric acid cycle, is the second stage of cellular respiration, a three-stage process by which living cells break down organic fuel molecules in the presence of oxygen to harvest energy they need to grow and divide. Specifically, IDH catalyzes the rate-limiting, irreversible, oxidative decarboxylation of isocitrate to produce: i) (D)-α-ketoglutaric acid (α-KG), ii) nicotinamide adenine dinucleotide + hydrogen (NADH) (2.5 adenosine triphosphate [ATP]), and iii) carbon dioxide. There are 3 isoforms of IDH enzyme in the human: 1) IDH1 in cytoplasm, 2) IDH2 in mitochondria, and 3) IDH3 in mitochondria (Thall 1994, Wang 2013, Yonal-Hindilerden 2016, Yoshihara 2001).

2.1.2.1 Mutations of IDH

IDH mutation plays a major role in carcinogenesis. Mutation of normal IDH enzymes, in particular, IDH1 and IDH2 (IDH3 has not been associated with mutation), leads to loss of physiological functions of these IDH enzymes. The resultant mutant IDHs (mIDHs) acquire new metabolic capabilities, that is, the catalytic metabolism of α-KG into oncogenic metabolite (*R*)-2-hydroxyglutaric acid (2-HG) (Dang 2009, Fathi 2012). Intracellular accumulation of 2-HG leads to a series of epigenetic changes, including hypermethylation of deoxyribonucleic acid (DNA) and histones proteins, which causes a blockade of cell differentiation and the consequent malignant transformation and proliferation of tumor cells (Chowdhury 2011, Ivanova 2005, Koivunen 2012, Xu 2011).

2.1.2.2 Mutations and Malignancies

Mutant IDHs have been found in multiple tumors, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasm (MPN), angio-immunoblastic T-cell lymphoma (AITL), glioma, chondrosarcoma, and cholangiocarcinoma (Delahousse 2018, Haferlach 2008, Harding 2018, Odejide 2014, Parsons 2008, Kosmider 2010, Marcucci 2010, Papaemmanuil 2016, Pardanani 2010, Yan 2009). Pharmacological intervention and therapeutic targeting of mIDH should therefore be logical in the treatment of certain cancers. Hematological malignancies (such as AML, AITL, and MDS) and solid tumors (such as primary brain cancer [Grade 2/3 glioma], secondary glioblastoma, chondrosarcoma, and cholangiocarcinoma) are tumor types with a documented high incidence of recurrent expression of mIDH.

The clinical efficacy of the FDA-approved single-target inhibitors ivosidenib and enasidenib for IDH1 or IDH2 mutations, respectively, has been validated in patients with relapsed or refractory AML that harbor corresponding IDH mutation (Stein 2017, Devillier 2015, DiNardo 2018). Ivosidenib is approved for newly diagnosed patients with AML who are ≥75 years old or who have

comorbidities that preclude the use of intensive induction chemotherapy (Roboz 2020). Patients who fail IDH inhibitor therapies do not have any standard treatment options available (NCCN-AML 2021).

2.1.2.3 Rationale and Benefits of Targeting All mIDHs Simultaneously

Mutant IDHs can co-exist and co-mutate concurrently and in any combination in patients with advanced relapsed, refractory, or resistant hematological malignancies. For example, some AML patients expressed co-mutations of different combinations of mIDH concurrently. In addition, mIDH isoform switching leading to resistance has been reported where patients become resistant to IDH1 inhibitor by upregulating and over-expressing other isotypes of mIDH, specifically mIDH2. Conversely, resistance to IDH2 inhibitor occurred when tumor cells upregulated and over-expressed other isotypes of mIDH, in this case mIDH1. Therefore, selective and single mIDH isotype inhibitors such as ivosidenib for mIDH1 or enasidenib for mIDH2 are not ideal or adequate and thus lead to unacceptable and insufficient efficacy, and above all, resistance (Choe 2019, Yang 2015).

Clinical development of an inhibitor such as HMPL-306 that targets, inhibits, and suppresses multiple mIDHs concurrently could lead to significant and durable clinical benefit.

HMPL-306 is a novel, orally available, small-molecule, highly selective, and potent inhibitor of IDH1 and IDH2 mutants. It demonstrated remarkable inhibitory effect on 2-HG in tumor cells with any IDH mutations, and therefore, this phase 1, open-label study is planned to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HMPL-306 in patients with advanced, relapsed, refractory, or resistant hematological malignancies that harbor IDH mutations.

2.2 Background

As of 23 October 2023, the dose escalation part of the current study has enrolled CCI patients with IDH mutations at increasing dose levels from CCI mg CCI mg once daily (QD). CCI [redacted] All of the patients enrolled in the dose escalation part were relapsed or refractory acute myeloid leukemia (R/R AML) patients. The study did not enroll any patients with myelodysplastic syndrome (MDS) or angio-immunoblastic T-cell Lymphoma (AITL), 2 other populations targeted for the originally planned expansion cohorts (Cohorts B and C) per Protocol 2020-306-GLOB1 Amendment 4.

Among the R/R AML patients, clinical responses were noted in patients who were naïve to prior IDH therapy at HMPL-306 doses of CCI mg QD or higher. CCI [redacted] were enrolled in the lower dose cohorts (CCI mg QD) making it difficult to evaluate efficacy and safety of HMPL-306 in this subgroup of patients with a high unmet need for active subsequent therapy.

The primary purpose of Amendment 5 is to modify the dose expansion cohorts based upon the sponsor's strategic evaluation of the unmet need and the ability to enroll in selected populations.

In Expansion Cohort A, the study will enroll 10 R/R AML patients, limited to patients who have received prior IDH inhibitor therapy (eg, enasidenib, ivosidenib, or olutasidenib). The safety and

proof of activity will be evaluated at the highest tolerable dose level evaluated in the dose escalation part (CCI mg QD). If proof of activity is established at the higher dose level in this high-risk population, further evaluation at lower doses may be warranted in future.

Expansion Cohorts B (MDS) and C (AITL) are removed, as these patients were not evaluated in the dose escalation due to lack of enrollment in these populations.

2.2.1 Description of HMPL-306

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

2.2.2 Supportive Nonclinical Data

2.2.2.1 Pharmacology

2.2.2.1.1 In vitro Pharmacodynamics

At the cellular level, using in vitro experiments in cell lines that contain mIDHs [CCI, IDH1R132H, IDH2R140Q, and IDH2R172K], HMPL-306 significantly inhibited production of 2-HG and showed a strong inhibitory effect on these mIDHs.

HMPL-306 has CCI effect on CCI (at the concentration of CCI μM, the inhibition rate was CCI) or on 322 kinases in the SelectScreen™ platform (at the concentration of CCI μM), showing high kinase selectivity. On the CEREP platform, HMPL-306 did CCI μM). Compared to the reference compound AG-221, HMPL-306 showed greater selectivity.

In cell functional studies, HMPL-306 suppressed production of 2-HG by inhibiting these mIDHs [CCI, IDH1R132H, IDH2R140Q, and IDH2R172K]. This leads to differentiation of tumor cells from immature malignant cells to mature normal cells.

2.2.2.1.2 In vivo Pharmacology

Target inhibition effect of 2-HG with HMPL-306 in U87MG-IDH2R140Q-M31 tumor model

In single-dose administration studies, various patient-derived xenograft tumor models that contained mIDH were used. At a CCI mg/kg, in all mIDH models used, the study drug maintained sustained suppression of 2-HG production at >95% from 16 to 24 hours; this effect became stronger after 24 hours and reached 98%, a near-complete inhibition of all mIDHs used in these studies.

In CCI studies, the inhibitory effect of HMPL-306 on 2-HG production after oral administration of HMPL-306 at CCI mg/kg CCI was investigated in a tumor model that contained mIDH. The results showed that after CCI of dosing, within 2 to 24 hours after the last dose, the inhibitory rate of HMPL-306 on 2-HG was maintained at more than 96% for all 3 dosages, and the inhibitory rate was significantly higher

than that CCI . Increase in 2-HG inhibition rate was due to an increase in drug exposure and target engagement (TE) after repeated administration.

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

In the IDH1 mutation tumor model HT1080 (R132C mutation), HMPL-306 was administered at CCI mg/kg, and the target inhibition of HMPL-306 on IDH1 mutation was evaluated by measuring changes of 2-HG levels after 2 to 40 hours. The results showed that at 16 and 24 hours after dosing in all 3 dose groups, the inhibitory rate of HMPL-306 against 2-HG in tumor tissues reached more than 90%, and CCI mg/kg CCI achieved almost complete inhibition (97% to 98%) at 16 to 24 hours.

The target inhibitory effect of HMPL-306 on 2-HG was further assessed in the HT1080 tumor model. After CCI mg/kg CCI, 2-HG inhibition rate in tumor tissues reached 97%, and its inhibitory effect on the target was stronger with the increase in drug exposure and TE after CCI doses.

2.2.2.1.3 Safety Pharmacology

The effect of HMPL-306 on hERG potassium channels was evaluated using HEK293 cell line. The half-maximal inhibitory concentration of HMPL-306 was CCI μM on hERG potassium channels, CCI .

CCI in unrestrained and telemetered Beagle dogs at single doses up to CCI mg/kg, the highest dose employed, further supporting a low risk of HMPL-306 on the cardiovascular system.

Single doses up to CCI mg/kg, the highest dose used, were administered via oral gavage to Sprague-Dawley rats. CCI .

Collectively, the results of the safety pharmacology studies indicate that HMPL-306 is low risk to the cardiovascular, respiratory, and central nervous system.

2.2.2.2 Pharmacokinetics

HMPL-306 has good in vitro permeability and is not a substrate of efflux transporters. Clearance of HMPL-306 in rats and dogs was CCI . CCI

HMPL-306 is stably metabolized in in vitro CCI in various species, and the major in vitro metabolite observed was the CCI . In vitro glucuronyl transferase study results showed that CCI were the main metabolic enzymes that mediate the generation of glucuronic acid conjugate.

In vitro studies showed that HMPL-306 exhibits a relatively CCI . HMPL-306 showed relatively CCI . HMPL-306 has an CCI

CCI [redacted]. HMPL-306 CCI [redacted]. HMPL-306 is CCI [redacted].

2.2.2.3 Toxicology

The completed HMPL-306 toxicology studies included single-dose toxicity studies in rats and dogs, 4-week repeat-dose toxicity studies with an 8-week recovery period in rats and dogs, genotoxicity studies (bacterial reverse mutation test, in vitro chromosomal aberration test, and an in vivo micronucleus test), and a phototoxicity study in rats. The results showed that single-dose administrations of HMPL-306 in rats and dogs were CCI [redacted] with maximum tolerated doses of CCI [redacted] mg/kg and CCI [redacted] mg/kg, respectively.

In the 4-week repeat-dose toxicity studies of rats and dogs, CCI [redacted] was observed in either of the 2 species. In the rats, CCI [redacted] were observed. There were CCI [redacted] observed in the dogs. The common target organ was CCI [redacted]. Changes in the CCI [redacted] were also observed at the high dose of rats at the end of the dosing period. After the 8-week recovery period, CCI [redacted] was still observed in the high-dose female rats, and all of the other aforementioned changes recovered.

HMPL-306 was not CCI [redacted].

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

2.2.3 Supportive Clinical Data

A phase 1 study is currently ongoing in China to evaluate safety, tolerability, and preliminary anti-tumor activity of HMPL-306 in patients with advanced hematological malignancies that harbor mIDH1/2 (NCT04272957). Refer to the latest HMPL-306 IB for the most updated clinical data summary.

2.3 Benefit/Risk Assessment

2.3.1 Benefit-Risk Assessment

The patients to be enrolled in this study will be those with advanced, relapsed, refractory, or resistant hematological malignancies and, therefore, have an unmet medical need.

For patients with refractory AML, the median overall survival (OS) is approximately 1.5 months with only 8% one-year survival (Gale 2008, Giles 2005). National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) practice guidelines recommend considering clinical trial for patients with primary refractory AML (NCCN-AML 2021, Heuser 2020). In the event that no clinical trial is available, then the intent of a second salvage chemotherapy in these patients, however, is only supportive at best. Therefore, patients with AML who have received at least 2 prior lines of therapy do not have a viable

treatment option available. Additionally, AML patients who fail IDH inhibitor therapies do not have any standard treatment options available, making them a population with very high unmet need (NCCN-AML 2021).

High-risk MDS (HR-MDS) carries a major risk of progression to AML and short survival. There are no standard treatment options for patients with relapsed or refractory HR-MDS. Patients ineligible for allo-HSCT have no approved second-line treatment options after failure of an approved hypomethylating agent (HMA), and clinical trials are the recommended option as per NCCN and ESMO guidelines (NCCN-MDS 2021, ELN 2017, Fenaux 2020).

Similarly, ESMO and NCCN practice guidelines recommend considering clinical trial for patients with relapsed or refractory AITL because of the poor survival rate with available single agent palliative therapy options (NCCN-MDS 2021, NCCN-PTCL 2021, d'Amore 2015).

HMPL-306 is a dual inhibitor of IDH1 and IDH2, which, in preclinical studies, has demonstrated similar efficacy to single target IDH inhibitors (ivosidenib and enasidenib), and may have similar benefit to other IDH1 and/or IDH2 inhibitors in the same class. Preclinical studies, including toxicology studies, indicate that HMPL-306 is well tolerated. Additionally, there are no approved therapies for the treatment of hematological malignancies that have been previously treated with an mIDH1 or mIDH2 inhibitor, thus providing a potential treatment option in an area of unmet medical need.

Most toxicities associated with the use of FDA-approved IDH1 and IDH2 inhibitors are considered to be mild and are well managed. Incidence of Grade 3 and Grade 4 events have been observed to occur at a lower frequency with these agents compared to other available treatments for AML. The most common toxicities associated with IDH1 and IDH2 inhibitors include differentiation syndrome, tumor lysis syndrome, hyperbilirubinemia, anemia, febrile neutropenia, thrombocytopenia, fatigue, nausea, and diarrhea (Stein 2017, DiNardo 2018). The incidence rate and severity of toxicities in these FDA approved IDH1 and IDH2 inhibitors is consistent with the safety profile of HMPL-306 in patients with hematologic malignancies. Further details on identified and potential risks of HMPL-306 are provided in the Investigator's Brochure (IB).

Taking into account the measures taken to minimize risk to patients in this study as defined in Section 7.4, Section 7.5, Section 7.6, and Appendix 11, the risks identified in association with HMPL-306 are justified by the anticipated benefits that may be afforded to patients with solid tumors with IDH mutations as defined in Section 5.2.

In summary, patients with AML who have received at least 2 prior lines of therapy including IDH inhibitors and patients with AITL and HR-MDS who have received at least 1 prior line of therapy do not have viable treatment options. This study provides an opportunity for these patients to participate in a study of HMPL-306, a novel agent that targets mutations that are common among these tumors. Thus, HMPL-306 can potentially provide clinical benefit to patients with advanced, relapsed, refractory, or resistant hematological malignancies.

Refer to the latest HMPL-306 IB for the most updated clinical and safety data.

3 OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are summarized in Table 3.

Table 3 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary	Part 1: To evaluate the safety and tolerability of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	MTD and/or RP2D Safety, including DLTs, TEAEs, SAEs, deaths, ECGs, and clinical laboratory abnormalities
	Part 2: 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, ORR, TTR, DoR, CBR, PFS, OS, DFS, EFS, and postbaseline transfusion independence
	To assess the PK of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	Observed plasma concentrations and exposure parameters of HMPL-306
	To assess PD of HMPL-306 in patients with advanced hematological malignancies that harbor IDH mutations	Observed plasma concentrations of 2-HG
Exploratory	To explore relationships between changes in frequency of genetic mutation, 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 exposure, TE, 2-HG levels, and percent inhibition	
	To explore the influence of genetic abnormalities other than IDH mutations on safety, efficacy, PD and 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; PK=pharmacokinetics; PD=pharmacodynamics; PFS=progression-free survival; PR=partial response; RP2D=recommended phase 2 dose; SAE=serious adverse event; SD=stable disease; TE=target engagement; TEAE=treatment-emergent adverse event; TTR=time to response.

4 STUDY PLAN

4.1 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).

4.1.1 Part 1 (Dose Escalation)

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 recommended phase 2 dose (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 dose-limiting toxicity (DLT) rate of 20% with an equivalence interval of 15% to 25%.

Like the 3+3 design, the mTPI-2 method incorporates prespecified escalation rules that can be presented in a table (Table 5). As shown in Table 5, the number of patients dosed at a given dose level are shown in the columns, while the rows indicate the number of DLTs experienced. The escalation/de-escalation rules from the table will be used for each dose level evaluated; the patient numbers and DLTs do not carry over from cohort to cohort. As an example, within a cohort:

- If none of the 3 patients experience a DLT→escalate the dose ("E" at column 3 row 0) to the next dose level cohort.
- If 1 out of 3 patients experience a DLT→de-escalate to a lower dose level ("D" at column 3 row 1).
- If 2 out of 3 patients experience a DLT→the dose is determined to be unacceptably toxic and will not be used again, de-escalate to a lower dose level ("DU" at column 3 row 2).
- If 1 out of 5 patients experience a DLT→stay at the same dose level ("S" at column 5 row 1).

The following rules apply during dose escalation:

- Starting dose at Cohort 1 is [redacted] mg.
- Although in the mTPI-2 method the cohort size is not fixed, at least 3 patients will be enrolled at each dose level. When all patients at a dose level complete DLT assessment, the study will escalate to the next dose level and another minimum of 3 patients will be recruited in this order until RP2D or MTD (Table 5).
- The sample size of a dose cohort that has already passed the preliminary DLT assessment (3 to 6 patients) and shown efficacy (eg, to include other efficacy signal for each tumor type) can be extended to 12 patients in order to further evaluate the safety and efficacy signals of that particular dose.

- If agreed upon by the investigators and the sponsor (eg, based on safety, PK, exposure, and TE and/or PD data from prior and current cohorts) that increasing the dose further may not yield additional benefit, the dose may stay at the current dose level, be de-escalated to any dose, or no future escalation may be made, even if the rule indicates "E" to escalate.
- Before MTD is reached, if PK evidence suggests the dose-exposure and TE relationship is saturated, dose escalation may be discontinued.
- The need for dose escalation to a specific dose beyond CCI mg QD or de-escalation to an intermediate dose level will be evaluated jointly by investigators and the sponsor based on cumulative clinical safety, PK, and preliminary efficacy data.

The stopping rules for this portion of the study are defined in Section 6.2.2.

PK week: The PK week is defined as 7 days prior to cycle 1 day 1 (C1D1), during which a single dose of HMPL-306 will be administered on Day 1 of PK week (Day - 7 relative to C1D1). Serial blood samples will be collected from Days 1 to 7 of the PK week for analysis of plasma concentrations of HMPL-306, 2-HG, and other biological markers as defined by the sponsor.

Study treatment: One 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 (see Table 4). The modified Fibonacci sequence will be used to increment the dose (see Table 5 for details on the dose escalation decision).

No DLTs or safety concerns were noted in dose levels 1 to 3. Based on the collective results of the preclinical in vitro and in vivo safety pharmacology, at a clinical dose of CCI mg, the risk for potential effects on the cardiovascular, respiratory, and central nervous systems is considered low after administration of HMPL-306.The anticipated human exposure (as determined by area under the curve [AUC]) at a clinical dose of CCI mg QD did not result in severe toxic findings in the 4-week toxicology studies and is expected to be well below the exposures at the highest doses studied. Please refer to the most recent IB for additional information.

Safety monitoring and evaluation of each dose escalation cohort will be carried out by the Safety Review Committee (SRC), which is comprised of the sponsor and investigators. The enrollment of dose levels 5 to 8 will be based on the cumulative safety and preliminary PK and PD data observed at CCI mg, and review will be conducted by the sponsor and the SRC members.

Table 4 Patient Dose Grouping, Dose Escalation Plan

Cohort #/Dose Level	Dose of HMPL-306 (PO QD with Water)
1	CCI mg
2	CCI mg
3	mg
4	mg
5	mg
6	mg
7	mg
8	mg

PO=orally; QD=once daily.
Note: Patients in dose escalation will receive 1 single-dose of HMPL-306 7 days prior to C1D1.

Table 5 mTPI-2 Decision Table for Dose Selection

Target toxicity probability: pT=20%; ε1=0.05; ε2=0.05

Number of Patients in a Cohort

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

E=escalate to the next higher dose; S=stay at the same dose; D=De-escalate to the previous lower dose; DLT=dose-limiting toxicity; DU=De-escalate to the previous lower dose and the current dose will not be used again in this study; MTD=maximum tolerated dose.
Note: The horizontal axis indicates the number of patients who are treated at the current dose and the longitudinal axis is the number of observed dose-limiting toxicities. ε1 and ε2 are fractions used to define an equivalence interval of MTD.

Safety Review Committee

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. The SRC will determine whether it is safe to continue to next predefined higher dose level, stay at the currently assigned dose level or whether the dose should be de-escalated to any lower dose, and finally, to determine RP2D based on evaluation of safety, PK, and PD data. The SRC, on an ongoing basis, will also monitor the benefit-risk of HMPL-306 treatment in the expansion cohort and make recommendations on the continuation of enrollment in the study.

Dose-Limiting Toxicity

DLT is defined as occurrence of any treatment-emergent adverse event (TEAE) as described in Section 8.1.3 during the DLT assessment window, unless clearly unrelated to the study drug as per investigator's discretion.

DLT Assessment Window:

For all patients in dose escalation, DLTs will be assessed during the DLT assessment window. This is the first 28 days of continuous study treatment (C1D1 through C1D28), and does not include the dose administered during PK week.

DLT-Evaluable Patient:

A patient is DLT-evaluable if the following criteria are met:

- has received at least 75% of the assigned dose of study drug during the DLT assessment window

  OR

- has not completed DLT assessment period due to a DLT

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

Patients who complete the DLT assessment window will be allowed to continue treatment until disease progression, intolerable toxicity, withdrawal of consent, lost to follow-up, end of study, conditions are met per Section 6.2.1, or death, whichever comes first.

Maximum Tolerated Dose

The MTD determination will be driven by the mTPI-2 method. The MTD will be any doses with true toxicity probability in the equivalence interval. For this study, the equivalence interval is defined as 15% to 25%.

Recommended Dose of the Expansion Cohort and Phase 2 Clinical Study (RP2D)

RP2D determination will take the following criteria under consideration:

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

4.1.2 Part 2 (Dose Expansion)

In the dose expansion part, HMPL-306 will be administered at the 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 depending on preliminary clinical response, safety signals, or operational feasibility. Patients who are not efficacy evaluable in any cohort may be replaced.

Study Treatment

Patients will receive HMPL-306 daily at CCI mg QD (highest tolerable dose evaluated in the dose escalation part) for 28-day cycles until disease progression, death, intolerable toxicity, withdrawal of consent, lost to follow-up, conditions are met per Section 6.2.1, or end of study, whichever comes first.

Safety Monitoring

Continuous safety monitoring for all enrolled patients will be carried out by participating investigators and the sponsor. The severity of all AEs will be graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

4.2 Design Rationale

4.2.1 Rationale for Starting Dose and Dosing Regimen

HMPL-306 is intended for use in patients with advanced relapsed, refractory, or resistant hematological malignancies. Hence, the starting dose is calculated based on the S9 guidelines from ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, using the HNSTD, and NOAEL dose (female). The calculation method is shown in Table 6 below:

Table 6 Starting Dose Calculation

	A 4-Week Study of HMPL-306 Orally Administered to SD Rats With an CCI Recovery Period	A 4-Week Study of HMPL-306 Orally Administered to Beagles With an CCI Recovery Period
Animal dose (mg/kg)	HNSTD ≥CCI	Female: NOAEL=CCI Male: HNSTD=CCI
Equivalent dose ratio converted based on body surface area (human/animal)	CCI	
Equivalent dose in human body converted based on body surface area (mg/kg/day)		
Equivalent dose in 60 kg of human body converted based on body surface area (mg/day)		
Initial dose calculated based on ICH S9 (mg/day)		
Proposed initial dose of phase I clinical trial (mg/day)		
Safety factor		

HNSTD=highest nonseverely toxic dose; ICH=International Council for Harmonization, NOAEL=no-observed-adverse-effect level; SD=Sprague-Dawley

The HNSTD was calculated from repeated dose toxicology studies in ruminant (rat) and non-ruminant (dog), and it showed safe doses obtained that were equivalent to human skin surface area dosages of CCI mg/day (rat) and CCI mg/day (dog). In accordance with ICH S9, the initial dose for first-in-human (FIH) study should be 1/10 of HNSTD in rats or 1/6 of HNSTD in dogs. Consequently, the starting dose calculated for the FIH study should be CCI mg/day or CCI mg/day. Nevertheless, initial dose for this FIH phase 1 clinical study is set at CCI mg QD PO. This provides a safety window of more than 14 times and about 39 times as calculated from the results of these studies in rats and dogs, respectively.

Furthermore, and in accordance with ICH S9, the dosing interval of the FIH study should be based on the dosing interval of nonclinical repeat-dose toxicity studies and the estimated half-life in the human body. The dosing interval of HMPL-306 in the 4-week repeated dose toxicity studies was QD. The estimated half-life of HMLP-306 was similar to that of approved products on market, which all use a regimen of QD. Therefore, a regimen of QD will be initially explored in this study. Exploration of another dosing regimen may be implemented, if indicated, based on analysis of emerging data.

4.2.2 Rationale for Study Population Selection

Mutations involving IDH enzymes play a role in the pathogenesis and development as subset of some hematological malignancies such as AML, MDS, MPN, and AITL. IDH mutations have been reported in 7% of MDS cases, 3% to 4% of MPN cases, and 20% to 30% of AITL cases

(Tefferi 2010, Breems 2008, Cairns 2012, Wang 2015, Yonal-Hindilerden 2016, Wang 2017). These mutations are critical in patient selection, clinical response, and even prognosis of these patients. Currently, ivosidenib (mIDH1 inhibitor) and enasidenib (mIDH2 inhibitor) are the only approved treatments available for patients in the United States with relapsed/refractory AML that harbor IDH1 and/or IDH2 mutations. Therefore, this study plans to enroll patients that harbor IDH mutations, co-mutation, or any combination thereof. Discussion of rationale including specific hematological malignancies for which IDH1 and/or IDH2 mutations play a role in some cases of disease, appears in the following sections.

4.2.2.1 Relapsed/Refractory Acute Myeloid Leukemia

This study plans to enroll AML patients who have received at least 1 prior line of therapy. The median overall survival for patients with refractory AML is 1.5 months with only 8% one-year survival (Giles 2005). Current guidelines recommend enrollment in a clinical trial for the management of relapse and/or refractory AML.

For patients with IDH mutations who are ineligible for standard chemotherapy and have failed standard of care first-line treatment (eg, low-dose cytarabine or HMA in combination with venetoclax), and for whom targeted therapy or salvage chemotherapy is not appropriate or have not had IDH isoform switching after prior treatment with IDH inhibitor, current guidelines recommend a clinical trial (NCCN-AML 2021, Heuser 2020).

Treatment options for primary refractory and relapsed AML in those patients who have undergone prior standard induction chemotherapy and consolidation, including allogeneic hematopoietic stem cell transplantation (allo-HSCT) and are not fit for further intensive or targeted treatment is limited. In the event that no clinical study is available, then the intent of second salvage chemotherapy in these patients, however, is only supportive at best.

Patients who have received at least 1 prior line of therapy, where an established standard of care with proven benefit for which the patient is eligible is not available at the time of enrollment, is an appropriate population for this 2020-306-GLOB1 study.

4.2.2.2 Relapsed/Refractory High-Risk Myelodysplastic Syndrome

This study plans to enroll HR-MDS patients who have relapsed after or are refractory to first-line treatment. High-risk MDS carries a major risk of progression to AML and short survival. Treatment options at diagnosis are limited to allo-HSCT, HMAs, and intensive chemotherapy (mainly intensive anthracycline-cytarabine combinations). For patients with HR-MDS who are not a candidate for intensive chemotherapy or allo-HSCT, HMAs are the only current approved treatment option. Once patients relapse or are refractory to an HMA, there is no approved second-line therapy, and the outlook is poor with a median survival of less than 6 months (Pratcorona 2013, Prebet 2011, Jabbour 2010) Clinical studies are, therefore, the recommended second-line option as per NCCN and ESMO guidelines (NCCN-MDS 2021, Fenaux 2020). For patients who are refractory to or have relapsed after allo-HSCT, clinical trials are also a recommended option as per the NCCN and ESMO guidelines. Therefore, patients with HR-MDS who have received at least 1 prior line of therapy are an appropriate population for this 2020-306-GLOB1 study.

4.2.2.3 Relapsed or Refractory Angio-immunoblastic T-cell Lymphoma

This study plans to enroll patients with AITL who have received at least 1 prior line of systemic anticancer therapy. For patients with relapsed/refractory (R/R) AITL, NCCN and ESMO clinical practice guidelines recommend considering a clinical study because of the poor overall survival with available salvage therapy options (NCCN-PTCL 2021, d'Amore 2015). Therefore, patients with R/R AITL who have received at least 1 prior line of therapy are an appropriate population for this 2020-306-GLOB1 study.

4.2.3 Rationale for Biomarker Testing

The mechanism of action of HMPL-306 is selective target inhibition of multiple isotypes of mIDH. Specifically, HMPL-306 is a highly selective, very potent inhibitor of mIDH. Results of local IDH mutation testing at screening will be used in further analyses.

CCI and CCI may be important metabolic enzymes for in vivo metabolism of HMPL-306. Therefore, mutation of CCI and CCI may affect PK, drug exposure, TE, and PD of the study drug. For this reason, samples collected will be tested for CCI and CCI as described in Section 6.1.17.

Mutant IDH isotypes (above) catalyze α-KG, and produce 2-HG – an oncogenic metabolite, accumulation of which plays a crucial role in pathogenesis of hematological malignancies in this patient population. Therefore, this study will monitor changes in levels of 2-HG in the blood. This may be useful for: i) PD and ii) correlation between PK, drug exposure, TE, and clinical response as specified in Table 1 and Section 6.1.15.

5 POPULATION

5.1 Definitions

Patients officially enter the Screening Period by signing the main informed consent either directly or via a legally authorized representative wherever permitted by local law.

An enrolled patient is one who has been deemed eligible without waiver of patient population criteria and has been assigned to a treatment group.

5.1.1 Informed Consent and Screening Period

5.1.1.1 Pre-Screening Period

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

Patients who fail pre-screening will have the following information recorded: demographic information, disease diagnosis, mIDH status results (if available), and reason for pre-screening failure.

5.1.1.2 Screening Period

Screening Period is defined as the period from main study consent until the first dose of HMPL-306 (Part 1: Day 1 of PK week, Part 2: C1D1).

A screen failure is a consented patient who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment. Screen failures may be rescreened.

Before informed consent is obtained, examinations for standard treatment performed within 28 days before planned C1D1 (60 days for ophthalmologic exams) can be used to replace assessments required for eligibility, except for assessments that need to be performed 7 days prior to study drug administration in the dose expansion part as specified in Table 2. For patients enrolled in dose escalation, all screening assessments must be completed before study drug administration on Day 1 of PK week.

5.1.1.3 Rescreening

Patients who cannot complete the procedures within the screening window may be rescreened, and certain screening procedures may not need to be repeated, including certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study, with documented sponsor approval.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, only after discussion with and permission from the HUTCHMED clinical research physician or designee.

Patients may be eligible for rescreening up to 2 times in any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment.

- Patients whose status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather or child illness).

Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

5.2 Inclusion Criteria

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

1. Patients aged ≥18 years.
2. Patients with advanced relapsed, refractory, or resistant hematological malignancies, as defined below:
   Part 1:
   a. Patients with documented IDH mutation per local or institutional next generation sequence (NGS).
   b. Patients must be refractory to or intolerant of established therapies known to provide clinical benefit.
   c. Patients who have received prior IDH inhibitor treatment may be enrolled in the escalation part of the protocol.
   Part 2:
   a. Patients with documented IDH mutation of any of these subsets: IDH1 (R132C), IDH1 (R132H), IDH2 (R140Q), and IDH2 (R172K), including co-mutations and any combination thereof per local or institutional NGS.
   b. Patients must have received at least 1 prior line of therapy. An established standard of care with proven benefit for which the patient is eligible, must not be available at the time of enrollment.
   c. Patients with R/R AML must have progressed on prior IDH treatment. Patients with AML must not have standard therapeutic options available (including IDH inhibitors where approved) and have the following:
      i. Relapsed AML unsuitable for intensive chemotherapy or venetoclax-based regimen or target agents;
      ii. Primary refractory AML unsuitable for intensive chemotherapy or venetoclax-based regimen or target agents.
   d. Patients with relapsed/refractory AML/ include the following:
      i. Subjects who relapse after transplantation;
      ii. Subjects in second or later relapse;
      iii. Subjects who are refractory to initial induction or re-induction treatment.
3. Patients must agree to bone marrow aspiration or biopsy performed before and during the treatment as specified in Appendix 1 (Part 1) or Appendix 2 (Part 2).
4. Patients must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2 (Appendix 3).

5. Patients must have adequate hepatic function as evidenced by: aspartate aminotransferase (AST), and alanine aminotransferase (ALT), ≤3.0 × upper limit of normal (ULN), unless considered due to leukemic disease and serum total bilirubin ≤1.5 × ULN.
6. Patients must have creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault formula.
7. Patients must recover to Grade <1 from any clinically relevant toxic effects of prior surgery, radiotherapy, or other therapies intended for the treatment of cancer.
8. Female patients of childbearing potential must have a negative serum pregnancy test within 7 days of study drug administration.
   NOTE: Postmenopausal is defined as at least 12 months of amenorrhea without alternative medical cause.
9. Male patients with partners of childbearing potential must agree to use a condom, and female patients of childbearing potential must agree to use highly effective form(s) of contraception that result in a low failure rate (<1% per year) when used consistently and correctly starting in the Screening Period, continuing throughout the entire study period, and for 30 days after taking the last dose of study drug. Such methods include combined hormonal contraception (estrogen/progestogen) associated with the inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomized partner, or sexual abstinence, if this is the normal and preferred lifestyle. Any hormonal method of highly effective contraception should always be combined with a condom because HMPL-306 may reduce their effectiveness.

5.3 Exclusion Criteria

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

1. Patients who have undergone hematopoietic stem cell transplantation (HSCT) within 60 days of the first dose of HMPL-306, or with clinically significant active graft-versus-host disease
2. Patients who received an investigational agent <14 days prior to their first day of study drug administration
3. Patients who are pregnant or breastfeeding
4. Patients with an active severe infection or with an unexplained fever >38.3°C during screening visits or on their first day of study drug administration (at the discretion of the Investigator, patients with an infection that is controlled with appropriate therapy are eligible); see Appendix 4 for coronavirus disease 2019 (COVID-19) risk assessment.
5. Patients with New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction <40% by echocardiogram (ECHO), or a multigated acquisition (MUGA) scan within approximately 28 days of C1D1 (Appendix 5)
6. Patients with a history of myocardial infarction within the last 6 months of screening
7. Patients with a known unstable or uncontrolled angina pectoris
8. Patients with congenital long QT syndrome or a known history of severe and/or uncontrolled ventricular arrhythmias
9. Electrocardiogram without any clinically significant findings, and for QT interval corrected for heart rate using Fridericia's formula (QTcF - interval from the start of the Q

wave to the end of the T wave [QT] corrected for heart rate using Fridericia's formula) interval >470 ms (for women) and >450 ms (for men), or other factors that increase the risk of QT prolongation or arrhythmic events and per the investigator's assessment

10. Patients taking medications that are known to prolong the QT interval (Appendix 6) NOTE: Patients may participate if medications are changed to acceptable alternatives
11. Patients with known active/untreated infection with human immunodeficiency virus (HIV), active hepatitis B virus (HBV), or hepatitis C virus (HCV)
12. Patients with immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation
13. Patients taking medications that can inhibit or induce CCI and/or CCI (Appendix 7) within 1 week or 5 half-lives (whichever is longer) before the start of study treatment
14. Patients who received small-molecule or large-molecule (such as antibody-based drug) drugs in previous clinical studies for <2 weeks, or <4 weeks, respectively, from the time of start of the study treatment to the last use
15. Patients with clinically significant, or severe gastrointestinal disease or condition that investigators suspect may affect drug absorption, including, but not limited to, active gastric and duodenal ulcers, ulcerative colitis and other digestive disease, gastrointestinal tumor with active bleeding, or other gastrointestinal conditions that may cause bleeding or perforation, by investigator's discretion
16. Patients with a clinically significant liver disease or condition such as Gilbert syndrome, and at the discretion of the investigator, may affect drug metabolism
17. Patients with a medical condition, physical examination finding, or clinical laboratory finding that, in the Investigator's opinion, contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications
18. Patients with a known hypersensitivity to HMPL-306 or to any of its excipients
19. Patients with presence of second primary malignant tumors within the last 2 years, with the exception of the following, if medically controlled: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and carcinoma in situ of the breast
20. Part 2 Only: The time since the last dose of prior IDH inhibitor treatment is within 30 days prior to the first day of study drug administration

6 STUDY CONDUCT

Recruitment is estimated to take approximately 18 months. The estimated duration for the entire study from the time the study is open to enrollment until completion of data analyses is approximately 36 months. During the study, assessments at each study visit will be performed as listed in Table 1 and Table 2 as described in this section.

6.1 Study Procedures

If there is dosing on assessment day, all assessment examinations must be completed before study drug administration, except for 12-lead electrocardiogram (ECG), ECHO/MUGA scan, ophthalmologic examination, and efficacy assessments.

6.1.1 Study Drug Administration

6.1.1.1 Dose Escalation

A single dose of HMPL-306 will be administered on Day 1 of PK week (Section 6.1.2) for each cohort in the dose escalation part. After PK week, all patients will receive continuous, daily administration of HMPL-306 beginning at C1D1.

6.1.1.2 Dose Expansion

All patients will receive continuous, daily administration of HMPL-306 at RP2D and/or MTD, beginning at C1D1.

6.1.2 PK Week

The PK week is defined as 7 days prior to C1D1 where a single dose of HMPL-306 will be administered on Day 1 of PK week (Day -7 relative to C1D1). Blood samples and ECG assessments will be collected at intervals as specified in Appendix 1. These samples will be analyzed for plasma concentrations of HMPL-306, 2-HG, and other biological markers as defined by the sponsor. PK week is applicable to every cohort in the dose escalation part only. See Appendix 1 for more details. PK week for a particular dose cohort will be considered optional and not mandatory if PK week data from 5 patients have been collected at the same dose.

6.1.3 Medical History and Demographic Information

Medical history data will be collected at Screening and will include significant clinical disease or symptoms, surgical history, history of malignancy (including date of diagnosis, classification, prognostic evaluation, treatment performed and outcome; tumor types and outcomes of any other previous malignancies), history of smoking, alcohol consumption, drug abuse, and other medically relevant history.

At pre-screening, only demographic information and diagnosis of disease will be collected. This demographic information will include gender, race, and in some countries, year of birth. If patients go on to participate in screening, demographic information on record will be used unless an update is warranted.

6.1.4 Prior and Concomitant Medications and Concomitant Procedures

Concomitant medications may include any prescription or over-the-counter (OTC) medications used by a patient. During the Screening Period, all medications taken by a patient within 28 days prior to HMPL-306 administration should be recorded in a case report form (CRF). At scheduled subsequent visits, any drugs taken during that period and within 30 days after end of treatment should be recorded in the CRF. Subsequent new transplantation pretreatment regimens and new antitumor treatment regimens, including HSCT, during the Safety and Efficacy Follow-up Periods will also be recorded. Prior and concomitant therapies are discussed in detail in Section 7.4.1 and Section 7.4.2.

6.1.5 Lifestyle Management

Patients enrolled in this study are advised to avoid unnecessary exposure to sunlight or any other source of ultraviolet light during their participation in this study through to 30 days after the end of treatment. Patients are encouraged to wear sunglasses and apply sunscreen products with a sun protective factor of at least 15. Safety of HMPL-306 under sunlight is not yet fully understood. Further nonclinical studies are planned to fully assess the phototoxicity effects of HMPL-306 in detail.

6.1.6 Vital Signs

Vital signs, including blood pressure, body temperature, heart rate, and respiratory rate, will be monitored as per Schedule of Events (Table 1 and Table 2). Patients need to sit still for 5 minutes before blood pressure measurement. Unscheduled examinations may be performed if clinically indicated.

6.1.7 Physical Examination, Weight, and Height

Physical examination and weight measurement will be conducted as per Schedule of Events (Table 1 and Table 2). Physical examination includes head, neck, ears, nose, eyes, throat, skin, mucous membranes, and gastrointestinal tract, as well as cardiovascular, renal, musculoskeletal, respiratory, and nervous systems.

Height will only be measured at screening.

6.1.8 ECOG Performance Status

ECOG PS scoring will be performed per Schedule of Events (Table 1 and Table 2). ECOG PS will be carefully scored in strict accordance with criteria (Appendix 3), especially to determine eligibility for enrollment.

6.1.9 Ophthalmologic Examination

Ophthalmologic examinations, including eye appearance, slit lamp examination, best corrected visual acuity, visual field, eye movement, pupil reflex, optical coherence tomography (OCT) examination, and intraocular pressure will be performed per Schedule of Events (Table 1 and Table 2). If a patient has undergone the relevant examinations 60 days before treatment (C1D1), they do not need to be repeated. After starting administration of the study drug, eye appearance and slit lamp examinations will be performed per Schedule of Events (Table 1 and Table 2). Other

ophthalmic examinations are to be performed if clinically indicated. If a patient develops an ophthalmic AE related to HMPL-306, the frequency of eye examinations should be increased to once per cycle until AE is resolved or stable. If retinal pigment epithelium (RPE) detachment is noted during an OCT examination, the patient may remain on the study drug with a follow-up OCT examination 2 weeks later. If RPE detachment is still observed during re-examination, the study drug dose should be reduced and an OCT examination performed again 2 weeks later. If RPE detachment is not resolving upon re-examination, the study drug dose should be further reduced or held until the RPE detachment is shown to be resolving.

6.1.10 Laboratory Evaluations

Laboratory assessments will be performed locally. The range of normal values of all study sites will be collected prior to start of the study.

6.1.10.1 Hematology – Routine

Hematology cell counts include red blood cells, platelets, reticulocytes, white blood cells and differentials (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), hemoglobin and hematocrit levels will all be performed per Schedule of Events (Table 1 and Table 2). Any additional routine blood tests during the study shall be arranged by the investigator on an as-needed basis.

6.1.10.2 Hematology – Blood Transfusion History and Blood Transfusion Record

Blood transfusion history, including red blood cell and/or platelet infusion within 8 weeks prior to HMPL-306 administration, will be recorded during Screening. The type of infusion, number of infusion unit(s), and date of infusion should be recorded. The pre-infusion hemoglobin level and/or platelet count should also be recorded if obtainable (either is acceptable, both are not required).

Blood transfusion record will include red blood cell and/or platelet infusion after the start of study drug administration until end of treatment (EOT) visit. The type of infusion, number of infusion unit(s), and date of infusion should be recorded. The pre-infusion hemoglobin level and/or platelet count should also be recorded if obtainable (either is acceptable, both are not required).

6.1.10.3 Hematology – Bone Marrow Aspiration and/or Biopsy

It is necessary to perform either bone marrow aspiration or biopsy, both are not mandatory. Patients with AITL that have fluorodeoxyglucose (FDG)-avid disease and will undergo positron emission tomography-computed tomography (PET-CT) imaging for screening and efficacy evaluation are not required to have a bone marrow aspiration or biopsy.

Bone marrow aspiration and/or biopsy examinations will be performed during screening, on Day 1 of Cycles 3, 5, and 7 (every 8 weeks ±7 days, for the first 24 weeks), then every 3 cycles (±14 days) thereafter (ie, Day 1 of Cycles 10, 13, and so on), at the EOT visit, and at every efficacy follow-up assessment for applicable patients. Additional bone marrow examinations may be performed at the investigator's discretion on as-needed basis.

Results of the analyses of the morphology examination, immunophenotyping, cytogenetics, and molecular genetic testing performed during screening will be collected in the electronic case report form (eCRF).

Please refer to Appendix 17 for a description of the immunophenotyping, cytogenetics, and molecular genetic testing for AML, HR-MDS, and AITL.

6.1.10.4 Blood Chemistry

Blood chemistry will all be performed per Schedule of Events (Table 1 and Table 2). This assessment should include blood urea nitrogen, creatinine, glomerular filtration rate, creatinine clearance rate; uric acid, electrolytes such as sodium, potassium, magnesium, chloride, calcium, and phosphorus, and glucose, creatine phosphokinase, and liver function tests such as total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP (alkaline phosphatase), lactate dehydrogenase, total protein, and albumin.

6.1.10.5 Blood Amylase and Lipase

Tests for blood amylase and lipase will be performed as per Schedule of Events (Table 1 and Table 2).

6.1.10.6 Fasting Lipid Panel

Fasting lipid panel, including total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides, will be performed as per Schedule of Events (Table 1 and Table 2).

6.1.10.7 Coagulation Indicators

Tests for coagulation indicators, including prothrombin time (PT), activated partial thromboplastin time, and international normalized rate (INR), will be performed as per Schedule of Events (Table 1 and Table 2).

6.1.10.8 HbA1C

Tests for glycated hemoglobin (HbA1C) will be performed as per Schedule of Events (Table 1 and Table 2).

6.1.10.9 Pregnancy Test

Female patients of childbearing potential (including those who have undergone tubal ligation) must undergo serum pregnancy test within 7 days of study drug administration (as well as prior to HMPL-306 administration on Day 1 of PK week in dose escalation) and record a negative result. After enrollment, serum or urine pregnancy test will be performed as per Schedule of Events (Table 1 and Table 2).

NOTE: Postmenopausal is defined as at least 12 months of amenorrhea without alternative medical cause.

6.1.10.10 Urinalysis

Urinalysis (or dipstick), including urine glucose, protein, ketone body, red blood cells, white blood cells (WBCs), and urobilinogen, will be performed as per Schedule of Events (Table 1 and Table 2).

6.1.10.11 Virological Screening

Viral serology should be tested at screening for all patients and includes HIV, HBV (HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb), cytomegalovirus (CMV) (CMV antibody), and HCV (HCV antibody). If HBsAg, HBcAb, or CMV antibody is positive, CMV DNA or HBV DNA is also required to be assayed by PCR method. If CMV DNA or HBV DNA is negative, patients may be enrolled and their CMV DNA or HBV DNA should be monitored every cycle. If HCV antibody is positive, HCV ribonucleic acid is required to undergo PCR testing.

6.1.10.12 IDH Mutational Status

Patients who have reports of positive mIDH status may directly enter Screening Period without pre-screening. Patients who have not been tested for mIDH should be tested locally (via biopsy tissue collection) to determine mIDH status before enrollment.

All patients will be required to provide samples for IDH mutational status confirmation as outlined in Section 6.1.16.

6.1.10.13 Tumoral Sample for Patients with AITL

Results of any analyses performed by local testing on previous tumoral samples taken for confirmation of PrD prior to screening or during screening, including immunophenotyping, cytogenetics, molecular genetic testing, and Epstein-Barr virus (EBV) status, will be collected in the eCRF.

Please refer to Appendix 17 for a description of the immunophenotyping, cytogenetics, and molecular genetic testing for AITL.

6.1.11 Electrocardiogram

The 12-lead ECG indicators include PR interval, QRS interval, RR interval, QT or QTcF, and heart rate. Evaluation time points are shown in Appendix 1 (dose escalation) and Appendix 2 (dose expansion).

6.1.12 Echocardiogram/Multigated Acquisition Scan

To evaluate ejection fraction of patients, ECHO (preferred method) or MUGA will be performed during the Screening Period, on Day 1 of every treatment cycle for the first 3 cycles, every other cycle thereafter, and at EOT visit. It is recommended to use the same assessment method throughout the study for each patient for consistent and uniform interpretation of the results.

6.1.13 Safety Evaluation

AEs emerging as a result of protocol-required procedure(s) are collected, even during pre-screening period if applicable. AEs are collected from the signing of the ICF until 30 days after the end of treatment or initiation of new antitumor therapy. Related AEs will be followed

until they are recovered to the baseline status, already in a stable state as assessed by the investigator, start of new antitumor therapy, lost to follow-up, death, withdrawal of informed consent, end of study, or it has been confirmed the AEs are unrelated to the study drug.

Serious adverse events (SAEs) are collected from the signing of the ICF (pre-screening ICF if applicable) until 30 days after the end of treatment or initiation of new antitumor therapy, whichever is earlier. After this 30-day period, and if the patient has not started any other antitumor treatment, investigators should report only SAEs considered to be related to the study drug.

6.1.14 Efficacy Evaluation

Efficacy evaluation of AML will be performed based on 2017 European LeukemiaNet (ELN) criteria (Appendix 8). Efficacy evaluation of HR-MDS will be performed based on the International Working Group response criteria in myelodysplasia (Appendix 12). Efficacy evaluation of AITL will be performed based on Lugano Classification (Cheson 2014) for Hodgkin and Non-Hodgkin's Lymphoma (Appendix 9).

Tumor evaluations will be conducted at screening, every 8 weeks (±7 days) during the first 24 weeks (ie, Day 1 of Cycles 3, 5, and 7), and every 12 weeks (±14 days) thereafter (ie, Day 1 of Cycles 10, 13, and so on) through EOT, or end of Efficacy Follow-up period (if applicable). Patients who discontinue HMPL-306 treatment due to reasons other than disease progression will continue tumor assessment according to previous tumor evaluation schedule until disease progression, as defined in Appendix 8 and Appendix 9, or start of new antineoplastic therapy (see Table 1). The same imaging procedure and laboratory tests used to define measurable lesions at baseline should be used throughout the study for each patient.

The baseline tumor assessment should be completed within 28 days prior to the first dose of study treatment (depending on the patient's disease status, a window may be acceptable based on a discussion between the investigator and the sponsor's medical monitor). Tumor assessments completed as standard of care, prior to signing of the informed consent and within 28 days of first dose of study treatment, may be used as baseline assessment.

Response evaluation of patients will be based on the most recent results of physical, bone marrow (if applicable), imaging, and hematological examinations, per local assessment. If a patient needs to delay the study drug after bone marrow examination and wait for recovery of peripheral blood count, then routine blood test results within 2 weeks after bone marrow analysis can be used to determine response.

For patients with myeloid malignancies, this assessment should be done using a blood test, bone marrow aspiration and/or biopsy, and physical examination as per the Schedule of Events (see Table 1).

For patients with hematological malignancies that are non-myeloid (eg, AITL), all measurable and evaluable lesions should be assessed and documented at screening and each subsequent efficacy evaluation using contrast-enhanced CT scans (neck, chest, abdomen, and pelvis) for non-FDG-avid disease and/or PET-CT scans for patients with FDG-avid disease. Enhanced magnetic resonance imaging (MRI) may be used instead of CT scans in patients for whom CT scans are contraindicated.

If a patient with non–FDG-avid disease has documented bone marrow involvement at screening, a bone marrow aspirate and/or biopsy will be required at each efficacy evaluation.

6.1.14.1 Risk Stratification/Prognostic Scoring

Prognostic stratification will be collected at screening as follows:

- AML: ELN Risk stratification by genetics (Appendix 15)
- HR-MDS: IPSS-R (Appendix 16)
- AITL: International Prognostic Index (Appendix 14)

6.1.14.2 Ann-Arbor Staging

Please refer to Appendix 13 for a description of Ann-Arbor staging for patients with AITL collected at screening.

6.1.15 Pharmacokinetics and Pharmacodynamic Evaluations

6.1.15.1 Sample Collection and Handling

Blood samples will be collected for PK and PD analysis of HMPL-306 and 2-HG levels in plasma, respectively. The full PK and PD evaluation schedule of dose escalation and expansion cohorts is presented in Appendix 1 and Appendix 2, respectively.

The collection, handling, and transportation of biological samples should be performed in accordance with required processes as provided in study-specific laboratory manual.

6.1.15.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of HMPL-306 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry method. Plasma samples will be analyzed to determine concentrations of 2-HG using a validated method.

Plasma samples may also be analyzed to document the presence of circulating metabolites of HMPL-306 using a qualified research method. If conducted, metabolite analysis will be reported outside of the clinical study report (CSR).

6.1.16 IDH Mutation Confirmation

Samples will be collected for central confirmation of mIDH status in order to validate local results and reports used by sites to determine eligibility for the study. Collected samples will follow specified procedures as indicated in laboratory manual. Bone marrow and/or whole blood will be collected for analysis as described in Appendix 1 (dose escalation) and Appendix 2 (dose expansion). This independent confirmation will use NGS by the central laboratory at prespecified intervals as determined by the sponsor. All samples should be prepared, labeled, handled, packaged, stored, and transported in accordance with required processes as provided in study-specific laboratory manual.

6.1.17 Exploratory Biomarker Evaluation

In this study, bone marrow and/or blood samples collected will be tested and analyzed for possible biologic marker(s) as specified/identified by the sponsor. Results from these tests and analysis of its data will be used to determine correlation between possible biomarkers of HMPL-306, hematological malignancies under study, and their relationship to PK, drug exposure, TE, PD, and clinical response, as well as potential mechanism of drug resistance.

Bone marrow/blood samples collected as per Appendix 1 (dose escalation) and Appendix 2 (dose expansion) will be tested further for a spectrum of levels and abundance of molecular mutations and genetic aberrations (as determined by the sponsor) to evaluate their association with all tumor types under study. Results from these tests, and the analyses thereof, will be used to further characterize and fully understand biological relationship between expression levels of these molecular mutations and genetic aberrations and their correlation to PK, drug exposure, TE, PD, and clinical response of HMPL-306, as well as potential mechanisms of drug resistance.

All related analyses will be performed by the central laboratory, and all samples should be prepared, labeled, handled, packaged, stored, and transported in accordance with required processes as provided in study-specific laboratory manual.

6.1.18 End of Treatment Visit

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

6.1.19 Follow-up Period

Safety Follow-up

All patients who have completed an EOT Visit will have a Safety Follow-up Visit. The Safety Follow-up Visit will be conducted at 30 days (±7 days) from EOT Visit.

AEs related to the study drug will be followed until resolution and SAEs will be followed until resolution regardless of the relationship to the study drug.

All female patients of childbearing potential must complete a pregnancy test (serum or urine) during the Safety Follow-up Visit. Pregnancy testing should be repeated for patients with suspected pregnancy. This is not applicable for postmenopausal female patients (defined as at least 12 months of amenorrhea without alternative medical cause), and the date of menopause should be recorded instead.

Efficacy Follow-up

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 per Section 6.2.1, or the end of the study, whichever comes first.

Survival Follow-up

All patients will be followed for survival status every 12 weeks (±14 days), until death, lost to follow-up, or withdrawal of consent. Survival information can be obtained via phone and information will be documented in the source documents and relevant CRFs.

6.1.20 End of Study

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.

6.2 Discontinuation or Withdrawal

6.2.1 Discontinuation of Treatment

6.2.1.1 Permanent Discontinuation of Treatment

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

Any patient who discontinues treatment should be encouraged to return to the study site for an EOT Visit and continue with the remaining study visits. The primary reason(s) for discontinuation must be recorded on appropriate CRF.

Patients must be discontinued from treatment for disease progression, withdrawal of consent, intolerable toxicity, as outlined in Table 8, Table 9, and Table 10, 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 may receive a maximum of 6 cycles of therapy unless the following are met:

- Patients with AML must have a partial response (PR) or better based on the 2017 ELN criteria (Appendix 8).
- Patients with HR-MDS must have a hematological response or better based on the IWG Criteria (Appendix 12)
- Patients with AITL must have a stable disease (SD) or better based on the Lugano Classification (Appendix 9).

6.2.1.2 Temporary Treatment Discontinuation

Patients who achieved adequate response after HMPL-306 treatment and meet other criteria for HSCT treatment can undergo HSCT after discontinuing HMPL-306 treatment, but they will continue to be retained in the study to perform efficacy follow-up and subsequent treatment recorded (Section 6.1.19). If the patient discontinues HMPL-306 treatment for HSCT treatment but eventually fails to receive HSCT treatment, HMPL-306 therapy can resume after sponsor approval; if the patient fails HSCT treatment and has recurrent hematological malignancy with mIDH and then HMPL-306 treatment can resume after request from the investigator and sponsor approval.

6.2.1.3 Withdrawal from Study

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

If a patient withdraws from the study, such a patient may request destruction of any samples taken and not tested. The investigator must also document requested destruction in the site study records.

6.2.1.4 Replacement of Patients

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

6.2.1.5 Patients Lost to Follow-up

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

Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with such patient (where possible, 3 telephone calls and, if necessary, a certified letter to patient's last known mailing address or local equivalent methods). These contact attempts should be documented in that patient's medical record. Should a patient continue to be unreachable, such patient will be considered withdrawn from the study.

6.2.2 Study Stopping Rules

Safety will be monitored continuously throughout the conduct of the study by a standing SRC. There will be periodic review of emerging data on safety, PK, drug exposure, TE, PD, and clinical response to determine continuation (or otherwise) of individual patient, cohorts, arms, or entire dose expansion part. If the study is halted as per Study Stopping Rules (Section 6.2.2.2) in either the dose escalation part or the dose expansion part, the study will only be restarted after Regulatory Approval as per local regulations.

Dose stopping rules for individual patients common to both dose escalation and dose expansion parts include:

1. DLTs that occur outside the DLT assessment window (DLT-equivalent) that have not resolved to Grade 1 or lower within 14 days, or after medical intervention as specified in Section 4.1.1.
2. Progression of disease that leads to treatment discontinuation
3. In the opinion and recommendation of the PI, or individual patient on their own, may withdraw from study at any time
4. If there is documented evidence of repeated non-compliance

6.2.2.1 Stopping Rules for Individual Patient

Dose Escalation:

Dosing will stop for an individual patient if:

DLT has not returned to Grade 1 or lower within 14 days

See Section 4.1.1 for details on dose escalation Part 1, DLT, and safety assessment.

Dose Expansion:

1. DLT-equivalent event has not resolved (even with medical intervention) within 14 days, or has re-occurred again at a de-escalated dose level
2. Resolution in severity (down-grade) and/or duration (within 14 days) of DLT-equivalent event will determine dose interruption, reduction, or discontinuation for the individual
3. Resolution of DLT-equivalent event will determine if the patient will resume treatment, at the discretion of investigator, at;

   the same dose level

   a lower dose

   discontinue treatment altogether

6.2.2.2 Stopping Rules for a Cohort or the Study

Dose Escalation Part

The stopping rules at a cohort level are based on mTPI-2 method and defined in Table 5. There will be no escalation to the next higher dose level cohort, until all available data from the current dose level cohort have been reviewed by SRC, who will then recommend appropriate dose escalation, de-escalation, or discontinuation.

This dose escalation part will be suspended, interrupted, or discontinued before MTD is attained based on:

1. Recommendation of SRC, and/or
2. Results of the analysis of emerging PK data suggesting that drug exposure or TE is saturated.

The dose escalation part of the study will prematurely end when any of the following conditions are met:

1. Excessive toxicity is present in the initial dose, ie, if DLT is observed in 1 out of 3 patients at the first dose level. If this occurs at the initial dose level, data will be reviewed by the SRC to determine next steps for the study.
2. Although no excessive toxicity is present in the first dose level cohort, if the dose returns to the initial dose according to the rules in Table 5 and excessive toxicity is present at the initial dose (for example, 2 or more patients with a DLT are observed in 6 patients).

Dose Expansion Part:

This part utilizes MTD or RP2D that has been determined as safe by SRC based on the conclusion of dose escalation part. The sponsor will periodically review evolving aggregate safety data by appropriate methods.

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6.3 Study Termination

The sponsor has the right to terminate study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate study, the investigator(s) will be notified in writing.

7 STUDY INTERVENTIONS

7.1 Study Drug Administration

Patients will receive HMPL-306 PO QD in a 28-day cycle.

Patients should take HMPL-306 on an empty stomach (no food 2 hours before and 2 hours after dosing) at a relatively fixed time every day with about 240 mL of water. The accurate actual time of dosing should be recorded in patient's pill diary each time.

The best effort should be exerted to ensure patients are medicated according to the study protocol. If the patient misses the study drug for more than 4 hours due to various reasons, it must not be supplemented. The missed dose must be recorded, and the drug will be continued at the next scheduled dosing time. The missed drug must be recorded. If vomiting occurs after drug administration, it should also be recorded, and the drug will be continued at the next scheduled dosing time.

Patients in dose escalation will receive a single dose of HMPL-306 for that cohort dose level, on Day 1 of PK week (7 days prior to C1D1).

7.1.1 Dose Escalation

In dose escalation, dosage will be according to dose level (see Table 4).

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

PK week: A single oral dose of HMPL-306 will be administered on Day 1 of the PK week (7 days prior to C1D1) for each dose level in dose escalation.

7.1.2 Dose Expansion

In dose expansion, HMPL-306 will be administered PO QD in a 28-day continuous dosing treatment cycle at CCI mg QD dose.

7.2 Description of Products

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

7.2.1 Formulation, Storage, Preparation, and Handling

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

HMPL-306 should be sealed and stored in a secure, limited-access area under appropriate conditions. Storage temperature should be between CCI °C and CCI °C with CCI . HMPL-306 should not be used beyond the expiration date provided by the sponsor.

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

7.2.2 Drug Accountability

7.2.2.1 Assignment/Disposal (Study Site)

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

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

Study drug will be disposed of at the study site according to the study site's institutional standard operating procedure or returned to HUTCHMED Limited or a HUTCHMED Limited-identified entity with appropriate documentation, as determined by the study site. If the study site chooses to destroy/dispose study drug, then the method of destruction/disposal must be documented.

7.2.2.2 Drug Return (Patient)

On Day -2 to Day 1, drug assignment will be performed. The first dose of study drug should be administered on C1D1, except for patients participating in escalation, where they will participate in a mandatory PK week and receive a single dose of HMPL-306 on Day 1 of PK week. Patients will be provided with a pill diary and be instructed on how to account for each day's dose appropriately. Patients should return all unused study drug and containers from the previous cycle on Day 1 (date of scheduled visits) of each subsequent cycle, and new study drug will be dispensed on same day. Site study staff should review patient's pill diary and provide a new diary if necessary on Day 1 visit of each cycle.

If a dose adjustment is required, the patient must return to study site and return all unused study drug. The site must log into the CRF, adjust the dose, reassign the drug serial number, and dispense new study drug dose to the patient. If dose is adjusted a second time, then the site must log into CRF and record the second dose adjustment. On this occasion, it is not necessary to reassign a new drug serial number. If tumor evaluation shows PrD during the previous cycle and the new drug has been dispensed, patient must return all unused study drug on 30-day (±7 days) safety visit after EOT.

7.3 Assessment and Verification of Compliance

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

7.4 Prior and Concomitant Therapies

7.4.1 Prohibited Therapies

Any therapy intended for cancer treatment (with exceptions in Section 7.4.2), whether currently marketed or experimental, is prohibited. This includes, but is not limited to, the following: chemotherapy, hormonal therapy, biologic therapy, radiotherapy, or herbal therapy.

Concomitant use of medications that have a known risk of causing QT prolongation (refer to Appendix 6), and/or torsades de pointes is prohibited.

HMPL-306 is a substrate of CCI . The potential effects of medications that affect PK of HMPL-306 via CCI pathways have not been tested in humans. Therefore, during treatment period, the use of inducers or inhibitors of CCI (Appendix 7) should be avoided, and such drugs should be discontinued at least 1 week or 5 half-lives (whichever is longer) before the start of study treatment. Prophylactic use of antiemetic drugs, granulocyte colony stimulating factors (G-CSF), platelet-activating factors, or erythropoietin is not allowed during the DLT assessment window. Outside the DLT assessment window, it may be allowed if the investigator considers it necessary.

7.4.2 Permitted Therapies

Concomitant therapy includes any prescription medications or OTC medications used by a patient. All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.

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

Patients with increased peripheral WBC count (WBC >25 × 10^9/L) and/or who develop differentiation syndrome (DS) during the study treatment period may receive hydroxyurea treatment to reduce peripheral WBCs. In addition, glucocorticoid treatment for DS is also allowed (Section 7.6.1).

Tumor lysis syndrome (TLS) is a potential serious complication of treatment, characterized by large amount of apoptosis or necrosis of tumor cells within a short time by treatment, causing cytological contents to be suddenly released to blood and cause metabolic abnormalities. Preventive medications for this syndrome should also be recorded in concomitant medication form.

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

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

7.4.3 Drug-Drug Interactions

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

CCI
.

During study treatment, the use of medications that are substrates of CCI (CCI) should be avoided. If the investigator believes it is necessary to use these medications, consent of the sponsor should be obtained before use, and close observation should be performed during use for probable reduction in efficacy or possible increase in likelihood of toxicity due to drug interactions.

In vitro data show that HMPL-306 has the potential CCI . Close and frequent monitoring of adverse reactions is recommended with concomitant use of any medication that is a CCI and has a narrow therapeutic index.

7.4.4 Rescue Therapies

Not applicable.

7.5 Dose Adjustments

7.5.1 Adjustment of Dose Within the DLT Assessment Window

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

- If a DLT occurs, HMPL-306 administration will be suspended and appropriate supportive treatment will be given.
- If a DLT returns to Grade 1 (inclusive) or lower within 14 days, HMPL-306 may be resumed at the previous lower dose if the investigator assesses that the patient may still benefit.
- If a DLT has not returned to Grade 1 (inclusive) or lower within 14 days, or DLT reoccurs at the lowered dose, HMPL-306 treatment will be terminated.
- If a patient experiences a Grade 4 nonhematologic toxicity, HMPL-306 treatment will be terminated.

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

Dose adjustments are to be made for any AE deemed at least possibly related to HMPL-306. Dose adjustments are to be made as outlined in Table 8 and Table 9.

Table 8 Dose Adjustment for Hematologic Toxicity

CTCAE v5.0 Grade	Action
Grade 1 or 2	None
Grade 3 or 4 (believed to be related to HMPL-306 and **NOT** underlying disease)	• Hold drug. • If the toxicity improves to Grade ≤2 within 7 days, then resume at original dose. • If the toxicity recurs at original dose, then resume 1 dose level lower provided the toxicity improves to Grade ≤2 within 7 days. • If the toxicity recurs in setting of prior dose level reduction, then resume 1 additional dose level lower provided the toxicity improves to Grade ≤2 within 7 days. • In the event the toxicity does not improve to Grade ≤2 within 7 days or toxicity recurs despite 2 dose reductions, HMPL-306 treatment is to be permanently discontinued.

CTCAE=Common Terminology Criteria for Adverse Events.

Table 9 Dose Adjustment for Nonhematologic Toxicity

CTCAE v5.0 Grade	Action
Grade 1 or 2	None
Grade 3	• Hold drug. • If the toxicity improves to Grade ≤2 within 7 days, then resume at original dose. • If the toxicity recurs at original dose, then resume 1 dose level lower provided the toxicity improves to Grade ≤2 within 7 days. • If the toxicity recurs in setting of prior dose level reduction, then resume 1 additional dose level lower provided the toxicity improves to Grade ≤2 within 7 days. • In the event the toxicity does not improve to Grade ≤2 within 7 days or toxicity recurs despite 2 dose reductions, HMPL-306 treatment is to be permanently discontinued.
Grade 4	Permanently discontinue treatment with HMPL-306.

CTCAE=Common Terminology Criteria for Adverse Events.

7.5.3 Dose Adjustment for QT Interval Prolongation

Table 10 Dose Adjustment for QT Interval Prolongation

Degree of QTcF Prolongation	Action
QTcF greater than 480 ms to 500 ms	• Hold drug. • Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTcF interval-prolonging effects. • Restart HMPL-306 at original dose if QTcF interval returns to less than or equal to 480 ms. • Monitor ECGs at least weekly for 2 weeks following resolution of QTcF prolongation.
QTcF greater than 500 ms and/or QTcF interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue HMPL-306 permanently. • Initiate continuous ECG monitoring and immediate clinical evaluation.

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

7.5.4 General Dose Adjustment Note

The severity of DLTs/AEs will be graded according to the NCI CTCAE v5.0. Reasons for dose modifications or delays, the supportive measures taken, and outcome should be documented in patient's chart and recorded in the CRF.

- For any concomitant conditions already apparent at baseline, dose modifications will apply according to corresponding shift in toxicity grade, if investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of 1 grade and treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by investigators to be unlikely to develop into serious or life-threatening events, treatment can be continued at the same dose.
- To recover from acute toxicity, unless otherwise indicated, treatment can be delayed for up to 14 days. If a treatment delay is required for 14 days or longer, treatment should be discontinued. Continuation/resumption of treatment after an interruption of 14 days or more must be discussed with the sponsor.
- Where several toxicities with different grades or severity occur at the same time, dose modifications should be according to highest grade observed.

7.6 Special Adverse Events Handling Principles

7.6.1 Differentiation Syndrome Handling Principles

Patients receiving HMPL-306 treatment are at risk of developing DS. According to relevant literature (Montesinos 2009), it is recommended that for patients with ≥2 items of the following

8 clinical symptoms, when related symptoms cannot be explained by other reasonable reasons, they should be diagnosed with DS and furthermore, in addition to grading as based on the NCI CTCAE v5.0, DS Montesinos grading also needs to be performed as per Table 11. The 8 clinical symptoms include unexplained fever, dyspnea, weight gain (>5 kg), unexplained hypotension, acute renal failure, interstitial lung infiltration, pleural effusion, or pericardial effusion. Symptoms, laboratory tests, or abnormal vital signs for each AE by name may be referred to in Table 11. Patients who do not meet aforementioned criteria but are assessed by the investigator to have suspected DS should also be reported as having DS (Section 8.1.4). For patients who have or are suspected of having developed DS, the investigator must report AEs as per the requirements in Section 8.2, for which patients should be closely monitored, and treated using following measures in a timely manner:

- Dexamethasone 10 mg and hemodynamic monitoring every 12 hours are immediately administered for at least 3 days or until symptoms disappear.
- Interrupt HMPL-306 if severe pulmonary symptoms requiring intubation or ventilator support and/or renal dysfunction persist for more than 48 hours after initiation of dexamethasone.
- Based on peripheral WBC count, hydroxyurea up to 2000 to 3000 mg twice daily (BID) is given orally for treatment.
- If clinically necessary, patient is given furosemide for treatment.
- Leukapheresis is performed if clinically necessary.

When the above treatment measures are unable to effectively control clinical features of DS, HMPL-306 treatment should be suspended. HMPL-306 administration can resume when signs and symptoms improve to Grade 2 or lower at a dose that should be decided after discussion with the sponsor.

Table 11 Differentiation Syndrome Diagnosis and Montesinos Grading Criteria

Diagnosis	**Montesinos Grading**	
	Moderate	**Severe**
Differentiation syndrome (≥2 symptoms)	2-3 symptoms	≥4 symptoms

Symptoms: Unexplained fever, dyspnea, weight gain (>5 kg), unexplained hypotension, acute renal failure, interstitial lung infiltration, pleural effusion, or pericardial effusion

7.6.2 Handling Principles for Noninfectious Leukocytosis

Noninfectious leukocytosis is defined as WBC >25 × 10^9/L or an absolute increase in total WBC of >15 × 10^9/L from baseline. Patients should be treated using following measures in a timely manner:

- Hydroxyurea oral therapy per institutional standards
- Leukapheresis is performed if clinically necessary

When above treatment measures are unable to effectively control the clinical symptoms, HMPL-306 treatment should be suspended. Prior to resuming study drug WBC should be <30 × 10^9/L in addition to resolution of clinical features of DS. After clinical features have been fully relieved, HMPL-306 administration can resume at a dose that should be decided after discussion with the sponsor.

8 SAFETY MONITORING

8.1 Definitions

8.1.1 Adverse Event

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

8.1.2 Serious Adverse Event

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

- Death.
- A life-threatening AE. An event is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- An abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, or ectopic pregnancy) in a child born to a female patient or female partner of a male patient exposed to study drug.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.1.3 Dose-Limiting Toxicity

DLT is defined as occurrence of any of the following TEAEs during the DLT assessment window, unless clearly unrelated to the study drug as per investigator's discretion:

- Nonhematologic toxicity:
  - TEAEs of Grade ≥4
  - Grade ≥3 with the exception of those that resolve within 72 hours of onset
- Hematologic toxicity, with the exception of neutropenia or thrombocytopenia that occurs with active leukemic disease:

- Grade 3 or 4 neutropenia lasting more than 7 days
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelets transfusion
- Grade 3 or greater febrile neutropenia defined as absolute neutrophil count 1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour

- Any TEAE requiring a dose delay of ≥14 days
- Cases of confirmed Hy's law

8.1.4 Adverse Events of Special Interest

All adverse events of special interest (AESIs) must be collected in the eCRF using the AESI option on the AE page of the eCRF. If they meet the seriousness criteria, they should also be reported as SAEs via the eCRF and SAE Report Form (see Section 8.1.2). Adverse events of special interest in this study include the following:

Differentiation syndrome

For patients who experience or have suspected DS, various symptoms and their NCI CTCAE v5.0 criteria grades should be recorded as an AE in the applicable eCRF (Appendix 11). Further, DS diagnosis time and gradation judged based on the NCI CTCAE v5.0 criteria in Table 11 should be recorded in the eCRF as Differentiation Syndrome.

Noninfectious leukocytosis

Noninfectious leukocytosis is defined as WBC >25 × 10^9/L or an absolute increase in total WBC of >15 × 10^9/L from baseline.

Potential drug-induced liver injury

According to Hy's law, ALT or AST elevations <3 × ULN accompanied by elevated total bilirubin (>2 × ULN) is considered as a sign of severe liver damage provided that cholestasis or other clinical jaundice causing hyperbilirubinemia are excluded. Therefore, the investigator must report AEs when elevation in ALT or AST levels during treatment are <3 × ULN and are accompanied by total bilirubin elevation to above 2 × ULN. The most appropriate diagnosis (when diagnosis cannot be confirmed) or laboratory abnormal values shall be recorded on the AE form of the eCRF and reported to the sponsor within 24 hours of learning of this event, regardless of whether it is an SAE or not.

8.2 Adverse Event Reporting

8.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, all AEs and SAEs regardless of attribution will be collected. After initiation of study drug, all SAEs and AEs regardless of attribution will be collected until 30 days after the end of treatment or start of a new antitumor therapy, whichever is earlier. After this 30-day period, and if the patient has not started any other antitumor treatment, then investigators should report only SAEs that are considered to be related to the study drug until study discontinuation.

8.2.2 Expedited Reporting

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events (both initial and follow-up) to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the sponsor within 24 hours after first learning of the event, regardless of relationship to study drug:

- SAEs
- Pregnancy
- Hy's Law

8.2.3 Dose-Limiting Toxicity Reporting

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

8.3 Eliciting Adverse Events

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

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

8.4 Assessment of Severity

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

For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of severity through clinical description by referring to the 5-grade determination standard in NCI CTCAE v5.0. Use the guidelines below for assessment of severity when observed or reported AE is not listed in the NCI CTCAE v5.0:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Note: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Note: Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.5 Causality Assessment

Investigators should use their knowledge of the patient, circumstances surrounding AE, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to study drug. To ensure consistency of causality assessments, investigators should apply general guidelines provided as below:

- **Related**: An AE is considered related if there is a reasonable possibility that the drug caused the AE. A 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. Factors used in this assessment include but are not limited to: There is a reasonable temporal relationship between AE and study drug; the AE resolves after de-challenge and/or AE recurs after re-challenge; the impact or presence of other contributing factors (eg, underlying study disease, medical conditions, concomitant medications) are either not present or ruled out; biological plausibility/mechanism of action of the study drug can explain the AE.
- **Unrelated**: If there is no reasonable possibility of correlation between an event and study drug, the AE will be deemed "unrelated" to study drug. Factors used in this assessment factor include but are not limited to: The AE(s) can be reasonably explained by the influence of underlying disease, or concurrent medical conditions, or other drugs; there is no temporal relationship between AEs and study drug; the AE worsens or does not improve after de-challenge; and/or the AE improves or does not recur after re-challenge.

8.6 Documenting Adverse Events

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

All AEs (including SAEs) should be recorded on the applicable CRF, and check box for "serious" should be ticked for entries that fit criteria for SAEs. Investigators must also complete an SAE report and submit this to the sponsor within 24 hours of knowledge of that event.

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

8.6.1 Diagnosis Versus Symptoms and Signs

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

8.6.2 Adverse Event Occurring Secondary to Other Events

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

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

8.6.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the CRF unless severity changes. If a persistent AE becomes more or less severe, it should be recorded again as a new CRF entry.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded in the CRF as separate events, respectively.

8.6.4 Abnormal Laboratory Values or Abnormal Vital Signs

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant by in the opinion of investigator

Investigators are responsible for reviewing all laboratory findings and abnormal vital signs and determining whether or not each abnormality should be reported as an AE.

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

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

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

8.6.5 Pre-existing Medical Condition

A pre-existing medical condition is one that is present at screening. Such conditions (not tumor type under study) should be recorded in the applicable CRF as medical history. A pre-existing medical condition should be recorded as an AE or SAE only if frequency, severity, or character of such condition worsens during study (excluding deterioration of study disease conditions). When such events are recorded in the CRF, it is important to convey the concept that such pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

8.6.6 Pregnancy

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

Male patients must also be instructed to inform the investigator immediately if their partner becomes pregnant during his participation in this study or within 30 days after the end of treatment. If such an event occurs, it should be reported as described above.

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

Any abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, or ectopic pregnancy) in a child born to a female patient or female partner of a male patient exposed to study drug should be recorded and reported as an SAE.

8.6.7 Progression of Hematological Malignancy Under Study

Events that clearly conform to expected progression of underlying disease should not be recorded as AEs. These data are only used for efficacy evaluation. Determination of clinical progression is at the discretion of the investigator and may include both objective and subjective data. The continuation decision should be made by the investigator in consultation with the sponsor. In most cases, expected mode of progression will be evaluated based on efficacy evaluation criteria suitable for studied tumor type. In a small number of cases, clinical progression is determined based on aggregation of clinical features. However, progression should be demonstrated using objective criteria. If it is uncertain whether a certain event is caused by progression of disease, it

should be reported as an AE. If such event leads to death, then it should be reported with reference to description of "Death" (see Section 8.6.8).

8.6.8 Death

All deaths that occur during protocol-specified AE reporting period must have their primary underlying cause reported to sponsor as an SAE with death listed as outcome. Deaths due to progression of disease must also be reported to the sponsor as an SAE. If primary cause of death is unknown at the time of reporting and/or if the death was unwitnessed, please record "death of unknown cause," or "unwitnessed death" in the eCRF and on the SAE report form. The eCRF and SAE report form should be updated when the cause of death has been determined. Death events that occur after 30 days following the end of treatment must be reported to the sponsor as an SAE only if it is confirmed as related to study drug.

8.6.9 Overdose

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

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

8.7 Duration of Follow-up for Adverse Events

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

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

All pregnancies that occur during participation in the study should be followed to determine their outcome.

9 ANALYSIS

9.1 Statistics and Analysis Method

All statistical analysis will be performed under the direction of sponsor's personnel. Details of statistical analysis and data reporting will be provided in Statistical Analysis Plan, which will be finalized prior to database lock.

The timing of analysis for each cohort may be different depending on completion of each cohort, and final analysis of study will be conducted at the time of analysis of last cohort. No formal interim analysis is planned. However, accrued data from any cohort may be analyzed for internal decision-making purposes; for example, to provide information for a potential phase 2 study design.

9.1.1 Statistical Hypothesis

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

9.1.2 Sample Size Rationale

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).

9.1.2.1 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 prespecified 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.

9.1.2.2 Dose Expansion Part

In order to better describe the safety of the recommended single-dose of HMPL-306 for future studies, approximately10 AML patients are expected to be treated with HMPL-306 in this part. For a given 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 CR rate is 20%, then 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.

9.1.3 Analysis Sets

The following analysis sets are defined for this study:

- Safety analysis set: All enrolled patients who received at least 1 dose of study treatment will be included in safety analysis population. Safety evaluation will be performed based

on first dose of study treatment received by a patient. This is the primary population for safety and efficacy analyses.

- DLT-evaluable analysis set: All patients enrolled in dose escalation part who are evaluable for DLT assessment. A patient is DLT-evaluable if such a patient meets the following criteria:
  - Has received at least 75% of the assigned dose of study drug during DLT assessment window
  - OR
  - Has not completed the DLT assessment period due to a DLT
- Response (efficacy) evaluable analysis set: All patients who receive study treatment and have a baseline tumor assessment, followed by at least 1 post-baseline assessment (usually after C3D1) will be considered evaluable for antitumor clinical response or efficacy endpoints.
- PK analysis set: All patients with at least 1 quantifiable plasma concentrations of HMPL-306 will be included in PK population analysis.
- PD analysis set: All patients with at least 1 quantifiable level of 2-HG in plasma will be included in PD population analysis.

9.2 Statistical Analysis

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

9.2.1 Patient Disposition

The number and percentage of patients that were enrolled in the study, treated, and discontinued from study treatment will be presented for the Safety Analysis Set. The primary reason for treatment discontinuation will be summarized according to the categories in the CRF. Patient disposition will be summarized overall and by cohorts.

Important protocol deviations will be summarized and listed by category.

9.2.2 Demographic and Other Baseline Characteristics

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

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

Other patient characteristics will be summarized as deemed appropriate.

9.2.3 Prior and Concomitant Medications

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

9.2.4 Safety Analysis

The summary of the exposure to study treatment, AEs, AESIs, AEs leading to drug modification or discontinuation including DLTs, changes in laboratory results, and changes in vital signs, etc, will be presented. The severity of all AEs will be graded according to NCI CTCAE v5.0, and the AE verbatim term will be coded by the Medical Dictionary for Regulatory Activities (MedDRA).

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

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

The following safety summaries will be produced:

- Overview of AEs
- Summary of DLTs (dose escalation part)
- Summary of TEAEs
- Summary of serious TEAEs
- Summary of AESIs
- Summary of TEAEs leading to dose interruption, dose reduction, or termination of treatment

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

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

For laboratory tests that are graded by NCI CTCAE v5.0 or higher, results will be summarized by grade. Treatment-emergent changes will be summarized by maximum post-baseline grade. A shift table summarizing the shift from baseline to maximum post-baseline grade will be presented.

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

9.2.5 Pharmacokinetics Analysis

Evaluation on PK will be performed on PK analysis set. Plasma concentrations of HMPL-306 will be tabulated and summarized using descriptive statistics (number of patients [n], arithmetic mean with standard deviation, coefficient of variation [CV%], and geometric mean, median, minimum, and maximum) as appropriate. PK parameters will be tabulated and summarized by treatment using descriptive statistics (number of patients, arithmetic mean with standard deviation, CV%, geometric mean, median, minimum, and maximum), as appropriate.

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

AUC_{0-t}	area under the plasma concentration-time curve from time 0 to time of the last measurable concentration
AUC_{0-inf}	area under the plasma concentration-time curve from time 0 to infinity
$AUC_{0-\tau}$	area under the plasma concentration-time curve within the dosing interval
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration (at steady state)
$C_{min,ss}$	minimum observed plasma concentration (at steady state)
C_{trough}	observed plasma concentration at the end of a dosing interval (taken directly before the next dose administration)
T_{max}	time to reach the maximum plasma concentration
C_{min}	minimum plasma concentration
$\%AUC_{ext}$	percentage of AUC_{0-inf} obtained by extrapolation
λ_Z	apparent first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the plasma concentration-time curve
$t_{1/2}$	associated with the terminal slope (λ_Z) of the semi-logarithmic drug concentration-time curve, calculated as $0.693/\lambda_Z$

CL/F	total plasma clearance of drug after extravascular administration, uncorrected for absolute bioavailability, calculated as dose/$AUC_{0\text{-}inf}$ after single dose or dose/$AUC_{0\text{-}\tau}$ after multiple doses
V_z/F	apparent volume of distribution
AR	accumulation ratio

Pharmacokinetic analysis will be performed using actual blood collection times relative to dosing times recorded in the raw data. If an actual blood collection time or a dosing time is missing, the nominal time may be used.

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

9.2.6 Pharmacodynamic Analysis

Levels of 2-HG in plasma will be tabulated and summarized using descriptive statistics (n, arithmetic mean with standard deviation, CV%, geometric mean, median, minimum, and maximum) as appropriate. Correlation between drug exposure level of HMPL-306 in plasma and 2-HG level and % inhibition in plasma will be analyzed using descriptive and graphical means.

9.2.7 Efficacy Analysis

Tumor assessment for patients with AML, HR-MDS, or AITL will be evaluated by the investigator according to the specific guidelines outlined in Section 9.2.7.1. However, the efficacy analysis will only be conducted for AML patients; for patients with HR-MDS or AITL, if enrolled, the tumor assessment data will be listed.

The following efficacy endpoints will be derived and analyzed using the safety analysis set for patients with AML:

- OS: defined as the time from the start of the study drug until death from any cause.
- Progression-free survival (PFS): defined as the time from the start of study treatment to disease progression, or death due to any cause, whichever occurs first.
- Baseline transfusion dependence: transfusions of red blood cells (RBCs) or platelets within 28 days prior to the first dose of treatment.
- Post-baseline transfusion independence (summarized through the following 2 ways):
  - No RBC or platelet transfusion for at least ≥4 weeks during treatment period; or
  - No RBC or platelet transfusion for at least ≥8 weeks during treatment period.

Patients with AML treated at the RP2D from Part 1 will be included in the data summary of the cohort in Part 2, unless otherwise specified. A patient data listing will be prepared for all patients.

Tumor response endpoints as defined in Section 9.2.7.1 (eg, best overall response, objective response rate [ORR], clinical benefit rate [CBR], and duration of response [DoR]) will be analyzed using the safety analysis set. For binary response endpoints such as ORR and CBR, the estimate and its 95% CI will be calculated using the Clopper-Pearson method for each cohort. The response (efficacy) evaluable analysis set will be used to conduct sensitivity analysis for tumor response.

For the time-to-event endpoints, such as PFS, OS, and DoR, the median, 25%, and 75% percentile of time-to-event will be estimated using Kaplan-Meier method with their corresponding 95% CI. Additionally, for PFS and OS, estimates will be provided for the survival probability along with their 95% CIs, which are calculated using linear transformation (Brookmeyer 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 will be calculated descriptively using the Kaplan-Meier method. In order to assess duration of follow-up for PFS and OS, Kaplan-Meier estimates will be calculated in the same way as in their analysis, while using a different censoring rule which reverses censoring indicator instead (ie, patients who have an event will be censored at the date of event). Patients who are censored will be assigned as an "event."

9.2.7.1 Tumor Response Endpoints for Patients with AML

Patients with AML will be evaluated according to the 2017 ELN criteria (Appendix 8). The antitumor efficacy endpoints will include the following:

- Best overall response (CR, complete response with negative minimal residual disease [CR_{MRD-}], CRi, CR with partial hematological recovery [CRh], morphologic leukemia-free state [MLFS], PR, SD, and PrD)
- ORR (including CR, CR_{MRD-}, CRi, CRh, MLFS, and PR)
- CBR: including ORR and SD
- Rate of CR + CRh (where CR was based on investigator assessment of response and CRh can be derived from relevant data including investigator-collected bone marrow and hematology data among responders)
- Duration of CR + CRh
- Time to CR + CRh
- Duration of CR
- Time to CR
- DoR
- Time to response (TTR)
- Disease-free survival (DFS): (Only for patients achieving CR or CR_{MRD-}, or CRi, or CRh) defined as the time from achieving response (CR or CR_{MRD-}, or CRi, or CRh) to disease relapse or death due to any cause
- Time to hematologic recurrence: (Only for patients achieving CR or CR_{MRD-}, or CRi, or CRh) defined as the time from when the patient achieves response for the first time (CR, CR_{MRD-}, CRi, or CRh) to disease recurrence

9.2.8 Exploratory/Biomarker Analysis

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

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

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

10.2 Ethics Review

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

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

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

The investigator will be responsible for the following:

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

10.3 Informed Consent

- Investigators or designees qualified by education, training, and experience to comply with GCP, and applicable regulatory requirements must obtain the signed ICF from patients prior to conducting any study-related procedures.
- The investigator or his/her representative will explain the nature of the study to the patient or to their legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- Patients must be informed that they may withdraw consent to participate in the study without any limitations. If the patient cannot sign the ICF, a legally acceptable representative of the patient must sign the ICF.
- If the patient and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the patient and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the patient and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.
- Informed consent should be recorded on the CRF.
- If the risk/benefit assessment changes after the safety analysis, the ICF needs to be reviewed and updated, and all updated information should be provided to patients (including patients who have already received the study drug).

10.4 Data Privacy

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

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

The investigator and the sponsor or its designee are responsible for ensuring that sensitive information, transfer of data/research samples, and storage of biological material retained for future research is handled in accordance with local requirements.

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

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

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

10.5 Disclosure

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

10.6 Data Quality Assurance

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

11 OVERSIGHT

11.1 Independent Monitoring

11.1.1 Safety Review Committee

- Patient safety will be continuously monitored by the SRC, which includes safety signal detection at any time during the study.
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to HMPL-306 administration. An initial safety review for this study is planned for the first 3 patients who are dosed and have provided safety data for 28 days after administration of Dose specified in Table 4 depending on the assigned cohort. The SRC, on an ongoing basis, will also monitor the benefit-risk of HMPL-306 treatment in the expansion cohort and make recommendations on the continuation of enrollment in the study.
- All safety data collected will be summarized and reviewed by the SRC for agreement of next steps.
- In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a requirement to re-evaluate the study.
    - Any deaths, regardless of causality.
    - In addition, safety data will be reviewed on an ongoing basis during study conduct. At a minimum of twice a year study data will be summarized and reviewed with investigators to identify potential safety signals. Additional safety review meetings may be scheduled based upon concerns of the sponsor or investigators.
- Enrollment will be paused during the review. If a stopping rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume. If the study is halted as per Study Stopping Rules in either the dose escalation part or the dose expansion part, the study will only be restarted after Regulatory Approval as per local regulations.

11.2 Quality Control and Assurance

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

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

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

11.2.1 Monitoring

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

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

11.2.2 Audits

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

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received and authorizing the sponsor's participation in the inspection.
- Providing access to all necessary facilities, study data, and documents for the inspection or audit.
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately.
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection.
- Documents patient to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also patient to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

11.2.3 Records

11.2.3.1 Data Capture and Management

The term CRF refers to the electronic data capture (EDC) system. The EDC system is the database where pertinent study data are collected. For all patients, including screen failures, data will be collected on source documents first. The principal investigator is responsible for assuring that the data entered into the CRF is complete, accurate, and that entry and updates are performed in a

timely manner. Some blood and bone marrow samples for PK, PD, and biomarkers assessments will be collected by study sites and sent to the designated central laboratory for processing, and analysis.

At all times, the principal investigator has final responsibility for accuracy and authenticity of all clinical and laboratory data entered in the EDC. Patient source documents are the investigator's patient records maintained at study site. In cases where source documents are the hospital or the physician's chart, the information collected in the EDC must match those charts. The completed pages of the EDC system are sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

11.2.3.2 Source Documentation

The investigator/institution should maintain accurate source documents and study records for all patients that support the information entered in the CRF.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable and not obscure the original entry.

All information recorded on CRFs must be traceable to source documents in the patient's file. Any changes should be explained if necessary (eg, via an audit trail).

11.2.3.3 Records Retention

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

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

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

11.3 Study Termination or Study Site Closure

The sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

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

Sponsor's Decision

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the appropriate regulatory authorities, and any CROs involved in the conduct of this study of any reason(s) leading to termination or suspension, as specified by applicable regulatory requirements. The investigator shall promptly inform all patients in their care and should ensure appropriate patient therapy and/or follow-up.

12 PUBLICATION POLICY

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

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

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

13 FINANCING AND INSURANCE

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

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15 APPENDICES

APPENDIX 1 PK/PD/BIOMARKER/ECG ASSESSMENTS FOR ESCALATION COHORTS

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Sample for PK	Blood Sample for 2-HG	Bone Marrow Sample for 2-HG	Blood and Bone Marrow Samples for Gene Mutation Analysis	ECG
Screening				X	X	X[2]	X
PK week Day 1	Predose[1]		X				X[3]
	0 h	X					
	0.5 h (±2 min)		X				
	1 h (±5 min)		X				X[3]
	2 h (±10 min)		X				X[3]
	3 h (±10 min)		X				
	4 h (±15 min)		X				X[3]
	6 h (±15 min)		X				
	8 h (±15 min)		X				
Day 2	24 h (±60 min)		X	X			
Day 3	48 h (±60 min)		X	X			
Day 4	72 h (±60 min)		X	X			
Day 5	96 h (±60 min)		X	X			
Day 6	120 h (±60 min)		X	X			
Day 7	144 h (±60 min)		X	X			
C1D1	Predose[1]		X	X			
	0h	X					
C1D8	Predose[1]		X	X			
	0 h	X					
C1D15	Predose[1]		X	X			
	0 h	X					
C1D22	Predose[1]		X	X			
	0 h	X					
C2D1	Predose[1]		X	X		X[2]	X[3]
	0 h	X					
	0.5 h (±2 min)		X				
	1 h (±5 min)		X				X[3]
	2 h (±10 min)		X				X[3]
	3 h (±10 min)		X				
	4 h (±15 min)		X				X[3]
	6 h (±15 min)		X				
	8 h (±15 min)		X				
C2D2	Predose[1]		X				
	0 h	X					
C2D8	Predose[1]		X	X			

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

2-HG=2-hydroxyglutaric acid; C=cycle; D=day; ECG=electrocardiogram; EOT=end of treatment; IDH=isocitrate dehydrogenase; PD=pharmacodynamic(s); PK=pharmacokinetic(s); CCI [redacted].

1 Blood sample collection should be performed within 30 minutes before the dosing on that day and approximately 24 (±60 minutes) hours after dosing on the previous day (ie, Day 1 of Cycles 1 or 2). Pre-dose bone marrow sample collection should be performed within 24 hours prior to dosing.

2 Bone marrow and/or whole blood will be collected for analysis of gene mutation abundance, such as IDH1, IDH2 (R140 and R172), DNMT3A, NPM1, SRSF2, RUNX1, NRAS, KRAS, ASXL1, TP53, FLT3, PTPN11, CCI [redacted], etc. Analysis for CCI [redacted] genes will be performed at baseline only.

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

APPENDIX 2 PK/PD/BIOMARKER/ECG ASSESSMENTS FOR EXPANSION COHORT

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Sample for PK	Blood Sample for 2-HG	Blood and Bone Marrow Samples for Gene Mutation Analysis	ECG
Screening				X	X[2]	X
C1D1	Predose[1]		X	X		X[3]
	0 h	X				
	0.5 h (±2 min)		X			
	1 h (±5 min)		X			X[3]
	2 h (±10 min)		X			X[3]
	3 h (±10 min)		X			
	4 h (±15 min)		X			X[3]
	6 h (±15 min)		X			
	8 h (±15 min)		X			
C1D2	Predose[1]		X			
	0h	X				
C1D8	Predose[1]		X	X		
	0 h	X				
C1D15	Predose[1]		X	X		
	0 h	X				
C1D22	Predose[1]		X	X		
	0 h	X				
C2D1	Predose[1]		X	X		X
	0 h	X				
C2D8	Predose[1]		X	X		
	0 h	X				
C2D15	Predose[1]		X	X		
	0 h	X				
C3D1	Predose[1]		X	X		X[3]
	0.5 h	X	X			
	1 h		X			X[3]
	2 h		X			X[3]
	3 h		X			
	4 h		X			X[3]
	6 h		X			
	8 h		X			
C3D2	Predose		X			
C5D1	Predose[1]		X	X		X
		X				
C7D1 and every 3 cycles thereafter	Predose[1]		X	X		X
	0 h	X				

Study Day	Time Relative to Dosing	Study Drug Intake	Blood Sample for PK	Blood Sample for 2-HG	Blood and Bone Marrow Samples for Gene Mutation Analysis	ECG
EOT (7 ±3 days after last dose)	Anytime			X		
Safety Follow-up visit (30 ±7 days after termination of treatment)	Anytime					X

2-HG=2-hydroxyglutaric acid; AITL=angio-immunoblastic T-cell lymphoma; C=cycle; D=day; ECG=electrocardiogram; EOT=end of treatment; IDH=isocitrate dehydrogenase; PD=pharmacodynamic(s); PK=pharmacokinetic(s); CCI [redacted].

1 Blood sample collection should be performed within 30 minutes before the dosing on that day and approximately 24 (±60 minutes) hours after dosing on the previous day (ie, Day 1 of Cycles 1 or 2). Pre-dose bone marrow sample collection should be performed within 24 hours prior to dosing.

2 Bone marrow and/or whole blood will be collected for analysis of gene mutation abundance, such as IDH1, IDH2 (R140 and R172), DNMT3A, NPM1, SRSF2, RUNX1, NRAS, KRAS, ASXL1, TP53, FLT3, PTPN11, CCI [redacted], etc. Analysis for CCI [redacted] genes will be performed at baseline only.

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

APPENDIX 3 ECOG PERFORMANCE STATUS

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

APPENDIX 4 COVID-19 RISK ASSESSMENT

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

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

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

1. Patient safety
    a. Patients will be educated by the investigator on COVID-19-related risks (ie, using cancer patient guidelines at ESMO web site). Instructions will be provided to the investigational site during the Study Initiation Visit.
    b. Minimize time patients spend at the clinic.
    - Blood sampling/visit may be performed at another location (if this can be done within local restrictions on social distancing) to reduce site burden and risk for infection, eg, local laboratory, home nurse, or opening a satellite site. The laboratory results must be reviewed by the investigator, the local laboratory included on the 1572, and laboratory normal ranges must be collected.
    - Study visits may be conducted with patients using telemedicine, where the investigator and site can videoconference with the patient. In this setting, investigators should perform as many assessments as possible, including any AEs, concomitant medications, and ECOG performance status.

    c. Reduce the risk for COVID-19 infection while traveling to and from the clinic by providing an option, where allowed, for car/taxi service to avoid public transportation.
    d. If a patient enrolled into the study subsequently tests positive for COVID-19, the data will be entered into the eCRF as an AE with proper source documentation.
2. Investigational Medicinal Product handling

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

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

   HUTCHMED Limited and its designee will adhere to all applicable regulatory authority requirements and country-specific guidelines for documenting and reporting any protocol deviations due to the COVID-19 pandemic. The deviations will be reported as instructed to the authorities and/or ECs.

4. Remote monitoring

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

5. COVID-19 Vaccine Guidance

   HUTCHMED Limited presents the following guidance on the administration of COVID-19 vaccines for patients on study.

   Patients who are enrolled on 2018-689-00US1 can receive currently approved (including Emergency Use Authorized [EUA]) inactivated vaccines based on investigator's clinical judgment. Given limited data, the possible interactions between the investigational drug and COVID-19 vaccines are unknown as this time.

   The following should be taken into consideration:

   - Follow any relevant regulatory guidelines which are applicable or may become applicable in your country or region
   - Administer only approved or EUA vaccines
   - Experimental and/or non-approved COVID-19 vaccines are prohibited per protocol
   - Report the vaccine name and batch number (if available) in the applicable eCRF
   - Record and follow any AEs related to the vaccine (including administration of) to resolution in the applicable eCRF

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

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

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

APPENDIX 5 NEW YORK HEART ASSOCIATION FUNCTION CLASSIFICATION

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

Source: New York Heart Association, Naming and Diagnostic Criteria for Cardiovascular Disease Version 9, Boston Mass: Little, Brown & Co; 1994: 253-256.

APPENDIX 6 PROHIBITED MEDICATION

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

Table 12 Medications That Can Prolong QT Interval

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

This is not an exhaustive list of drugs that can prolong QT intervals. The investigator should carefully consider the concomitant medication of each patient, assess the risk-benefit ratio, and perform appropriate monitoring.

APPENDIX 7 CCI [redacted]

CCI [redacted]

Note: This is not an exhaustive list containing all CCI [redacted] inhibitors/inducers. The investigator should carefully consider the concomitant medication of each patient, assess the risk-benefit ratio, and perform appropriate monitoring.
Source: https://www.drugbank.ca

APPENDIX 8 2017 EUROPEAN LEUKEMIANET EFFICACY CRITERIA FOR AML

Treatment Response	Efficacy Criteria
Complete response (CR)	• Myeloblast percentage <5% • Blast cells without Auer bodies • No blast cells in peripheral blood • No extramedullary lesion • ANC ≥1.0×10^9/L, PLT ≥100×10^9/L
Complete response with negative minimal residual disease (CR_{MRD-})	• CR with negative RT-qPCR or CR with negative MFC
Complete response with incomplete count recovery (CRi)	• Meets all other criteria of CR but ANC <1.0×10^9/L or PLT <100×10^9/L
Morphologically leukemia-free status (MLFS)[a]	• Myeloblast percentage <5% • Blast cells without Auer bodies • No extramedullary lesion • No hematological recovery requirements
Partial response (PR)	• Meets all hematological criteria for CR • The percentage of myeloblasts decreases from baseline by least 50% and reaches 5% to 25%
Stable disease (SD)[b]	• Fails to meet criteria for CR, CRi, CR_{MRD-}, MLFS, PR, or progressive disease
Progressive disease[c, d]	• Increase in bone marrow blast percentage and/or absolute peripheral blood blast cells – The percentage of myeloblasts increases from baseline by >50% (if blast cells at baseline are <30%, net increased value needs to be ≥15%); or percentage of myeloblasts >70% continues for at least 3 months; ANC is not seen to be improved by at least 100%, reaching (>0.5×10^9/L and/or PLT reaches >50×10^9/L, without blood transfusion); or – The absolute peripheral blood blast cell count (WBC×blast cell ratio) increases by >50% and reaches >25×10^9/L (without differentiation syndrome); or • New extramedullary diseases
Hematologic recurrence	• After achieving CR/CR_{MRD-}/CRi, ≥5% of the blast cells recur in the bone marrow; or • Blast cells occur in the peripheral blood; or • Extramedullary lesions occur

AML=acute myeloid leukemia; ANC=absolute neutrophil count; CR=complete response; MFC=multiparameter flow cytometry; PLT=platelet; RT-qPCR=quantitative reverse transcription polymerase chain reaction; WBC=white blood cell.

[a] Marrow should not merely be "aplastic"; at least 200 cells should be enumerated or cellularity should be at least 10%

[b] Period of stable disease should last at least 3 months

[c] Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD

[d] "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms:

Source: Döhner al 2017

APPENDIX 9 LUGANO RESPONSE CRITERIA FOR HODGKIN AND NON-HODGKIN'S LYMPHOMA

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response	**Complete Metabolic Response**	**Complete Radiologic Response (All of the Following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b]	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial Metabolic Response**	**Partial Remission (All of the Following)**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from	Not applicable

Response and Site	**PET-CT–Based Response**	**CT-Based Response**
	chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given for further evaluation with MRI or biopsy or an interval scan.	
No Response or Stable Disease	**No Metabolic Response**	**Stable Disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
PD	**Progressive Metabolic Disease**	**PD Requires at Least 1 of the Following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or Score 4 or 5 in any lesion with an increase in intensity of FDG uptake from baseline (and/or new FDG-avid foci consistent with lymphoma)	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: • LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir • 0.5 cm for lesions ≤2 cm and 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must

Response and Site	PET-CT–Based Response	CT-Based Response
		be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS=5-point scale, CT=computed tomography, FDG=fluorodeoxyglucose, IHC=immunohistochemistry, LDi=longest transverse diameter of a lesion, MRI=magnetic resonance imaging, PET=positron emission tomography, PPD=cross product of the LDi and perpendicular diameter, SDi=shortest axis perpendicular to the LDi, SPD=sum of the product of the perpendicular diameters for multiple lesions.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson 2014.

APPENDIX 10 LIST OF SUBSTRATES OF CCI [redacted]

CCI [redacted]

CCI [redacted].

Note: CCI [redacted]. The investigator should carefully consider the concomitant medication of each patient, assess the risk-benefit ratio and perform appropriate monitoring.

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

APPENDIX 11 Differentiation Syndrome Symptoms and the Names of Possible Included Adverse Events, Laboratory Tests, or Vital Signs Abnormalities

Symptoms	Names of Possible Included Adverse Events, Laboratory Tests, or Vital Signs Abnormalities
Unexplained fever	Fever, febrile neutropenia, or body temperature ≥38.3°C, etc.
Dyspnea	Acute respiratory failure, heart and lung failure, cardiopulmonary distress, cough, dyspnea, respiratory distress, respiratory failure, or respiratory arrest, etc.
Weight gain (>5 kg)	Capillary leakage, fluid retention, excessive body fluid, systemic edema, excessive blood volume, increased blood volume, edema, peripheral edema, or weight gain >5 kg from baseline
Unexplained hypotension	Hypotension or systolic blood pressure <90 mmHg, etc.
Acute renal failure	Acute kidney injury, anuria, cardiorenal syndrome, liver and kidney failure, prerenal failure, renal failure, acute renal failure, renal insufficiency, kidney injury, or serum creatinine increased from baseline and is >26.52 μmol/L or increased to 1.5 times that of baseline
Interstitial lung infiltration or pericardial effusion	Acute pulmonary edema, acute respiratory distress syndrome, non-cardiogenic pulmonary edema, pulmonary edema, pulmonary congestion, pleural effusion, pericardial effusion, acute interstitial pneumonia, acute lung injury, atypical pneumonia, lower respiratory tract infection, pulmonary infection, pulmonary infiltration, pneumonia, pulmonary toxicity, etc.

APPENDIX 12 INTERNATIONAL WORKING GROUP RESPONSE CRITERIA IN MYELODYSPLASIA

Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS

Category	Response Criteria (Responses Must be at Least 4 Weeks)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥ 11 g/dL Platelets ≥ 100 × 109/L Neutrophils ≥ 1.0 × 109/L† Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥50% over pretreatment but still >5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥50% increase in blasts to >5% blasts 5%-10% blasts: ≥50% increase to >10% blasts 10%-20% blasts: ≥50% increase to >20% blasts 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥2 g/dL Transfusion dependence

Proposed Modified International Working Group Response Criteria for Altering Natural History of MDS (Continued)

Survival	Endpoints: Overall: death from any cause Event-free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

AML=acute myeloid leukemia; CR=complete remission; DFS=disease-free survival; FAB=French-American British; HI=hematologic improvement; Hgb=hemoglobin; IWG=International Working Group; MDS=myelodysplastic syndromes; PFS=progression-free survival; PR=partial remission.

Note: Deletions to IWG response criteria are not shown. To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

*Dysplastic changes should consider the normal range of dysplastic changes (modification) (Ramos 1999).

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Source: Cheson 2006

Proposed Modified International Working Group Response Criteria for Hematologic Improvement

Hematologic Improvement*	**Response Criteria (Responses Must Last for at Least 8 Weeks)†**
Erythroid response (pretreatment, <11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 week compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤9.0 g/dL Pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, $<100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $>20 \times 10^9$/L platelets Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100%†
Neutrophil response (pretreatment, $<1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $>0.5 \times 10^9$/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥1.5 g/dL Transfusion dependence

HI=hematologic improvement; Hgb=hemoglobin; IWG=International Working Group; RBC=red blood cell.

Note: Deletions to the IWG response criteria are not shown.

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).

†Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

Source: Cheson 2006

APPENDIX 13 ANN-ARBOR STAGING

Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Note: Extent of disease is determined by positron emission tomography– computerized tomography for avid lymphomas and computerized tomography for non-avid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

[a] Whether Stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Source: Cheson 2014

APPENDIX 14 INTERNATIONAL PROGNOSTIC INDEX

International Prognostic Index

Risk Factors	IPI Risk Group	Number of IPI Risk Factors
Ann-Arbor Stage III or IV Age >60 years Serum LDH >1×ULN ECOG Performance Status ≥2 Extranodal involvement ≥2	Low	0 or 1
	Low-intermediate	2
	High-intermediate	3
	High	4-5

ECOG=Eastern Cooperative Oncology Group; FDG-PET=fluorodeoxyglucose-positron emission tomography; IPI=International Prognostic Index; LDH=lactate dehydrogenase; ULN=upper limit of normal.

The results of FDG-PET should not be taken into account for calculation of IPI as this prognostic score was established without FDG-PET.

Source: Shipp 1993.

APPENDIX 15 2017 ELN RISK STRATIFICATION BY GENETICS

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low}† Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high}† Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡ Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) 25 or del(5q); 27; 217/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type NPM1 and FLT3-ITD^{high}† Mutated RUNX1¶ Mutated ASXL1¶ Mutated TP53#

AML=acute myeloid leukemia; ELN=European Leukemia Net; HCT=Hematopoietic cell transplantation; WHO=World Health Organization.

Note: Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of FLT3-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "FLT3-ITD" divided by area under the curve "FLT3- wild type"; recent studies indicate that AML with NPM1 mutation and FLT3-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT (Gale 2008, Pratcorona 2013,Schlenk 2014, Ho 2016).

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1.

‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML) (Breems 2008).

¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

#TP53 mutations are significantly associated with AML with complex and monosomal karyotype (Papaemmanuil 2016, Haferlach 2008, Bowen 2009, Rücker 2012, Devillier 2015).

Source: ELN 2017

APPENDIX 16 INTERNATIONAL PROGNOSTIC SCORING SYSTEM REVISED PROGNOSTIC SCORE VALUES

IPSS-R Prognostic Score Values

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM Blast, %	≤ 2	—	>2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

ANC=absolute neutrophil count; BM=bone marrow.
— indicates not applicable
Source: Greenberg 2012.

APPENDIX 17 IMMUNOPHENOTYPING, CYTOGENETICS, and MOLECULAR GENETICS

Acute Myeloid Leukemia(AML)	
Immunophenotyping	CD34; CD117; CD33; CD65; CD14; CD36; CD64; CD41; CD61; CD235a; CD36; HLA-DR
Cytogenetics	inv(16); t(16;16); del (16q); t(8;21); t(15;17); +8; t(9;11); -5/del (5q) -7/ del(7q); t (4;11); inv(3); t (3;3); t(6;9); t(9;22); Abn 3q; Abn 9q; del (20q); del (21q); del (17p); +6; -Y; del (12p)
Molecular genetics	CEBPA; FLT3-ITD; FLT3-TKD; KIT; NPM1; RUNX1; NRAS; KRAS; MLL; PML-RARA; ASXL1; JAK2; BCOR; DNMT3A;TP53; SF3B1; TET2; SRSF2; PTPN11

Myelodysplastic Syndrome (MDS)	
Immunophenotyping	CD34; CD117; CD33; CD65; CD14; CD36; CD64; CD41; CD61; CD235a; CD36; HLA-DR
Cytogenetics	-5 or del (5q); -7 or del(7q); i(17q) or t(17p); del(12p) or t(12p); del(11q); -13 or del(13q); del(9q); Idic(X)(q13); Inv(3)(q21q26.2) ;t(6;9)(p23;q34) t(3:21)(q26.2;q22.1); t(1;3)(p36.3;q21.2) ;t(11:16)(q23;p13.3); t(2;11)(p21;q23)
Molecular genetics	JAK2 V617F; JAK3; CALR;MPL; NRAS; KRAS; PTPN11; NF1; FLT3; CSF3R; CBL; KIT; TET2; ASXL1; DNMT3A; UTX; EZH2; SETBP1; SF3B1; U2AF1; SRSF2; NPM1; TP53; RUNX1

Angio-immunoblastic T-cell lymphoma (AITL)	
Immunophenotyping	CD3; Loss of CD3; CD7; Loss of surface CD7; sCD3(/dim)/CD4+/CD10; CD20 ; CD4; CD8; CD21; CD23; CD28; CD10; CD2; CD5; CD7; CD30; CD200; CD279
Cytogenetics	Trisomy 3; Trisomy 5; Trisomy 21; Additional X chromosome; Loss of 6q ; T(5;9)(q33;q22);ITK-SYK
Molecular genetics	TET2; DNMT3A; RHOA; PLCG1; FYN; VAV1 ; RHOAG17V; BCL6; PD1; ICOS; PAX5; SAP; C-MAF; CXCL13; CXCR5; Plasma cell light chain restriction [κ and λ]
EBV viral load	EBV Viral titer

APPENDIX 18 Amendment History

Amendment 4 (24 June 2022)

Section Number	Summary of Change	Rationale for Change
Title Page, Footers, Signature Page, and Globally	Updated the sponsor company name, address, and logo where appropriate throughout.	The administrative updates were made to appropriately reflect the change of sponsor company name.
Synopsis	Language in the description of sites was updated to indicate approximately 40 study sites in Europe, Asia Pacific, and the United States.	The description of sites updates was made to be consistent with the description in other study trials.
	Language in target population was updated to remove "after at least 2 lines of therapies" and updated the sentence to "Patients with acute myeloid leukemia (AML) (Cohort A) and who have received at least 2 prior lines of therapy and patients with high-risk myelodysplastic syndrome (HR-MDS) (Cohort B) and angio-immunoblastic T-cell lymphoma (AITL) (Cohort C) who have received at least 1 prior line of therapy."	The language updates for the target population were made to provide clarity of eligible patient populations and lines of therapy.
Synopsis, Section 1.2 – Study Schematic, and Section 4.1.1 – Part 1 (Dose Escalation), Table 4 – Patient Dose Grouping, Dose Escalation Plan	Part 1 dose escalation language was updated to reflect the addition of dose levels 5, 6, 7, and 8, or CCI [redacted] mg dose levels, respectively.	The updates were made to further investigate tolerability, pharmacokinetic (PK) exposure and pharmacodynamic (PD) effects at higher dose levels.
Synopsis and Section 3 – Objectives and Endpoints	Language was updated in the secondary endpoint to summarize the endpoints.	The language updates to the secondary endpoints were made to reflect changes to the statistics section for clarity.
Synopsis, Section 1.2 – Study Schematic, Section 2.3.1 – Benefit-Risk Assessment, Section 4.1.2 – Part 2 (Dose Expansion), Section 4.2.2.2 – Cohort B: Relapsed/Refractory High-Risk Myelodysplastic Syndrome, Section 6.1.14 – Efficacy Evaluation, Section 6.2.1.1 – Permanent Discontinuation of Treatment, Section 14 – References, and Appendix 9 – 2015 IWG Criteria for Measurement of Treatment Response in Adult MDS/MPN	Language was updated to remove myeloproliferative neoplasm (MPN) from Cohort B and the requirement for at least 2 prior lines of therapy for high-risk myelodysplastic syndrome (HR-MDS). Associated language was also updated; including, but not limited to the following: • Language was added to clarify that no approved second-line therapy exists for patients with HR-MDS that are relapsed or refractory to hypomethylating agents (HMAs) and are not eligible for intensive chemotherapy or allogenic	The language was updated as the eligible patient population updates included the removal of MPN, hematological malignancies are not routinely tested for IDH (isocitrate dehydrogenase) mutations, nor do they frequently demonstrate IDH mutations. The number of approved second-line therapies was corrected.

Section Number	Summary of Change	Rationale for Change
	hematopoietic stem cell transplant (allo-HSCT). • Language was added to clarify that patients HR-MDS who have received at least 1 prior line of therapy do not have viable treatment options and are eligible for the 2020-306-GLOB1 study. • Appendix 9 and the Savona 2015 reference were removed.	
Synopsis and Section 4.2.2.3 Cohort C: Relapsed or Refractory Angio-immunoblastic T-cell Lymphoma	Language was updated to indicate that the study plans to enroll patients with AITL receiving at least 1 prior line of systemic therapy.	The language was updated as there is only 1 line of systemic therapy available to patients with AITL.
Synopsis, Section 1.2 – Study Schematic, Section 4.1.2 – Part 2 (Dose Expansion), Section 9.1.2 – Sample Size Rationale, and Section 9.1.2.2 – Dose Expansion Part	Language was updated to remove Cohort D from the study. Associated language was updated to reflect the removal of Cohort D, including, but not limited to the following: • The number of cohorts was reduced from 4 to 3 cohorts. • The approximate enrollment for Part 2 was reduced from 60 to 45 patients. • The probability of observing at least 1 adverse event (AE) was updated to reflect the change from 60 to 45 patients. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 AE in 45 patients is 99%, 90%, and 36%, respectively.	The language updates including and related to the removal of Cohort D are due to very few hematological malignancies outside of Cohorts A, B, and C having IDH mutations or receiving routine testing for IDH mutations.
Synopsis and Section 3 – Objectives and Endpoints	Language was added to the secondary objectives to include the complete response with partial hematological recovery (CRh).	The updates to the secondary objectives were made to reflect changes to efficacy response assessment for patients with AML.
Synopsis, Section 9.1.2 – Sample Size Rationale and Section 9.1.2.1 – Dose Escalation Part	Language was updated to reflect the updated approximate number of patient enrollment from 60 patients to approximately 75 patients. The dose escalation part estimate of evaluable patients was updated from 12 to approximately 15 patients to 24 to approximately 40 patients.	The updates were made to reflect the additional cohorts added to the dose escalation (Part 1).
Section 1.3 – Schedule of Events; Table 1 – Schedule of Events (Dose Escalation) and Table 2 –Schedule of Events (Dose Expansion)	Language was added to the Schedule of Events (SOE) to reflect the addition of Ann-Arbor staging and Risk stratification/Prognostic scoring at screening staging assessment. The	The updates to the SOE were for clarity and to reflect changes to study

Section Number	Summary of Change	Rationale for Change
	footnotes "w" and "x" were added in the Dose Escalation SOE and the footnotes "v" and "w" were added to the Dose Expansion SOE to provide further guidance on the Ann-Arbor staging and Risk stratification/Prognostic scoring assessments, respectively. Cycle 2 Day 1 (±1 week) Ophthalmologic examination was added, and the corresponding footnote was updated to include a description of the procedures. Additional collection of hematology, blood amylase and lipase, fasting lipid panel, coagulation indicators, HbA1c, and blood transfusion recording were added to safety follow-up visit.	assessments/data collection and per regulatory request.
Section 1.3 – Schedule of Events; Table 1 – Schedule of Events (Dose Escalation) and Table 2 – Schedule of Events (Dose Expansion), Section 6.1.10.3 – Hematology – Bone Marrow Aspiration and/or Biopsy, Section 6.1.10.13 – Tumoral Sample for Patients with AITL	Language and references were updated to indicate that bone marrow aspiration will include local immunophenotyping, cytogenetic analysis, and molecular testing in Table 1 footnote "o" and Table 2 footnote "n." Language was updated to provide procedural references located in Sections 6.1.10.3 and 6.1.10.13 and Appendix 17.	The updates to the bone marrow aspiration, immunophenotyping, cytogenetic analysis, and molecular testing were made to provide clarity to the process of collection and analysis.
Section 2.1.2.2 – Mutations and Malignancies and Section 14 – References	Language was added to indicate that ivosidenib was also approved for use in newly diagnosed patients with AML who are ≥75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. The corresponding reference (Roboz 2020) was added to the references and in-text citation.	The ivosidenib updates were made to reflect changes in Ivosidenib FDA approval accuracy.
Section 4.1.1 – Part 1 (Dose Escalation)	The language discussing the need for dose escalation "beyond CCI mg QD…" was updated to "beyond CCI mg QD…". The language that discusses the rationale behind the addition of dose levels 5 to 8 was added.	The updated language is to reflect the additional dose escalation cohorts up to CCI mg. Dose levels 5 to 8 rationale was added for clarity.
Section 4.1.1 – Part 1 (Dose Escalation), Section 6.2.1.4 – Replacement of Patients, and Section 9.1.2.1 – Dose Escalation Part	The language discussing whether patients who are not dose-limiting toxicity (DLT)-evaluable in a dose cohort "will" be replaced was updated to "may" be replaced.	The language update is to reflect the possibility that not all non-DLT-evaluable patients may be replaced.
Section 5.1.1.3 – Rescreening	Language and section were added to provide the possibility to rescreen patients who were unable to complete the procedures within the screening window, screen failed, or became eligible as the	The addition of rescreening language was to provide clarity and guidance on patient rescreening.

Section Number	Summary of Change	Rationale for Change
	result of an amendment, status change, or change in extenuating circumstances.	
Section 5.2 – Inclusion Criteria; Part 2	Language was added to "b" to clarify that patients with AML must have received at least 1 prior lines of therapy for their hematologic malignancy. Language was added to "e" to clarify the number and acceptable prior lines of therapy. Inclusion criterion 6 was added to indicate that patients with AITL must have measurable lesion as defined in Lugano 2014.	The updates to "b" and "e" were to clarify the number of lines of therapy and acceptable prior lines of therapy for each population. The addition of inclusion criterion 6 was to clarify the requirement of measurable lesions for patients with AITL.
Section 5.3 – Exclusion Criteria	Language for criterion 8 was updated to exclude patients with congenital long QT syndrome. Language for criterion 9 was updated to exclude patients with electrocardiogram results showing no clinically significant findings and a QTcF interval of >470 ms for women and >450 ms for men.	The language updates were made per regulatory request.
Section 6.1.10.3 – Hematology – Bone Marrow Aspiration and/or Biopsy and Appendix 17 – Immunophenotyping/Cytogenetics/ Molecular Genetics	Language was added to indicate that patients with AITL that have fluorodeoxyglucose (FDG)-avid disease and will undergo positron emission tomography-computed tomography (PET-CT) imaging for screening and efficacy evaluation are not required to have a bone marrow aspiration or biopsy. Language was added to indicate that the results of the analyses of the morphology examination, immunophenotyping, cytogenetics, and molecular genetic testing performed during screening will be collected in the electronic case report form (eCRF). Appendix 17 was added to provide a reference and description for immunophenotyping, cytogenetics, and molecular genetic testing for AML, HR-MDS, and AITL.	The language updates were made to provide references and guidance on assessment procedures and reporting requirements.
Section 6.1.10.11 – Virological Screening	Language was updated to indicate that viral serology testing should be done at screening for all patients.	The language was updated to provide clarity on the virology screening requirement.
Section 6.1.10.13 – Tumoral Sample for Patients with AITL	Section was added and language was included to indicate that the results of any analyses performed by local testing on previous tumoral samples taken for confirmation of progressive disease (PrD) prior to screening or during screening	The addition of this section and language is to provide guidance on reporting requirements of the results of previous tumor analysis in patients with AITL.

Section Number	Summary of Change	Rationale for Change
	including immunophenotyping, cytogenetics, molecular genetic testing, and Epstein-Barr virus (EBV) status will be collected in the eCRF.	
Section 6.1.14 – Efficacy Evaluation and Section 15 – Appendices; Appendix 12 – International Working Group (IWG) Response Criteria in Myelodysplasia	Language was added to indicate that the evaluation of HR-MDS will be performed based on IWG response criteria in myelodysplasia as indicated in the new Appendix 12. Language was removed indicating that all measurable and evaluable lesions should be assessed and documented at screening and each subsequent tumor evaluation. Language was added to indicate that for patients with hematological malignancies, all measurable and evaluable lesions should be assessed and documented at screening and each subsequent efficacy evaluation using contrast-enhanced CT scans for non-FDG-avid disease and/or PET-CT for patients with FDG-avid disease. Furthermore, patients with non–FDG-avid disease who have documented bone marrow involvement at screening, a bone marrow aspirate and/or biopsy will be required at each efficacy evaluation.	These language updates were made to provide clarity on the efficacy evaluation of patients with HR-MDS and AITL.
Section 6.1.14.1 – Risk Stratification/Prognostic Scoring	Section and language were added to define how AML, HR-MDS, and AITL prognostic stratification at screening will be collected.	These language updates were made to provide clarity on study assessments/data collection.
Section 6.1.14.2 – Ann-Arbor Staging	Section and language were added to provide guidance on Ann-Arbor staging.	The addition of this section and language was to reflect study assessments/data collection updates.
Section – 6.2.1.1 – Permanent Discontinuation of Treatment	Language was added to discuss patients with HR-MDS based on the IWG criteria. Language was removed with unspecific references to other hematological malignancies.	The language updates were made to describe and clarify the patient population and associated efficacy evaluation.
Section 7.1 – Study Drug Administration	Language was added to indicate course of action for patients missing a dose of study drug by more than 4 hours.	The language was added for guidance and clarity.
Section 7.2.1 – Formulation, Storage, Preparation, and Handling	Language was added to indicate that storage procedures for study drug should include protection from light and moisture.	The language was added for clarity and guidance.
Section 7.5.3 – Dose Adjustment for QT Interval Prolongation, Table 10	Language for Table 10 was updated to require discontinuation of HMPL-306 permanently in response to a QTcF greater than 500 ms.	The language updates were made per regulatory recommendation.

Section Number	Summary of Change	Rationale for Change
	Language was removed for QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.	
Section 8.1.4 – Adverse Event of Special Interest	Section and language added to discuss adverse events of special interest (AESIs). AESIs should be reported immediately. Differentiation Syndrome is an AESI and moved here from Section 8.6.4 for consistency.	The addition of this section and associated language was to provide guidance on AESIs.
Section 8.2.1 – Adverse Event Reporting Period	Language updated to indicate that AEs regardless of attribution will be collected until 37 days after last dose of study drug instead of 30.	The change in collection days was made to correct the length of collection.
Section 9.1.2.2 – Dose Expansion Part	Language was updated to indicate that more patients may be enrolled in this cohort if further analysis of safety and efficacy signals are needed.	This language was added for clarity on enrollment.
Section 9.2.4 – Safety Analysis	Language was updated to indicate that a summary of AESIs will be produced.	The addition of AESI summary was for consistency with other HUTCHMED protocols.
Section 9.2.7 – Efficacy Analysis	Language was extrapolated upon and updated for clarity.	The language changes were the updates made to the study eligible patient populations and associated efficacy evaluations for clarity.
Appendix 14 – International Prognostic Index	International Prognostic Index was added as Appendix 14.	The International Prognostic Index was added as an appendix for reference.

Amendment 3 (15 October 2021)

Section Number	Summary of Change	Rationale for Change
Section 2.2.2.1.3 – Safety Pharmacology	Language comparing the half-maximal HMPL-306 inhibition on hERG potassium channels with complete inhibition of 2-HG was changed to CCI [redacted] Language describing the negative result of the bacterial reverse mutation test and mammalian chromosome aberration test were removed. Language was updated describing the effects of HMPL-306 on telemetered Beagle dogs was updated to clarify that the CCI [redacted] mg/kg) showed low risk on the cardiovascular system.	Language updated for clarity.

Section Number	Summary of Change	Rationale for Change
	Language was added describing the effects of HMPL-306 on Sprague-Dawley rats was updated to clarify that the CCI mg/kg) showed no HMPL-306-related effects on the respiratory and central nervous system. Conclusion language was updated to describe the results of these pharmacology studies collectively indicating that HMPL-306 is low risk to the cardiovascular, respiratory, and central nervous system.	
Section 2.2.2.2 – Pharmacokinetics	Language was updated for general clarity. Language was added to indicate that HMPL-306 has an CCI . Language suggesting that HMPL-306 may CCI was removed.	Language updated for clarity.
Section 2.2.2.3 – Toxicology	Toxicology Section was moved from Section 2.2.2.2 to Section 2.2.2.3 to reflect CTD structure. Language was generally updated to more succinctly summarize the results of the completed HMPL-306 toxicology studies and to conclude that HMPL-306 was CCI	Updated with the results of the in vivo phototoxicity study and for clarity.
Section 2.2.3 – Supportive Clinical Data	Removed language describing current enrollment and status of dose limiting toxicities and instead refer the reader to the IB for the most current information.	Language updated for clarity.
Section 2.3.1 Benefit-Risk Assessment	Section 2.3.1 Risk Assessment heading was updated to Section 2.3.1 Benefit-Risk Assessment. Introductory language to Table 3 Summary of Potential Risks of HMPL-306 and Table 3 itself was removed. Section 2.3.2 Benefit Assessment heading was removed and the section language was incorporated under Section 2.3.1 Benefit-Risk heading. The subheading 'Overall Benefit/Risk Conclusion' was removed. Language was added describing toxicities associated with the use of FDA-approved IDH1 and IDH2 inhibitors and their incidences.	Due to limited human exposure, no adverse drug reactions of HMPL-306 have been identified as of Investigator Brochure (IB) version 3. Table 3, which contained theoretical effects of HMPL-306, is subject to change and/or become outdated annually based on updated human experience. The section has been updated to provide a high-level summary of benefits and risks associated with approved IDH inhibitors, while referring the reader to the IB for additional information.

Section Number	Summary of Change	Rationale for Change
	Summary language was moved to the end of the section and a reference to the IB for the most updated clinical data was added.	
Section 4.2.2 – Rationale for Study Population Selection Section 4.2.2.1 – Cohort A: Relapsed/Refractory Acute Myeloid Leukemia Section 4.2.2.2 – Cohort B: Relapsed/Refractory High-Risk Mylelodysplatic Syndrome/Myeloproliferative Neoplasm Section 4.2.2.3 – Cohort C: Relapsed or Refractory Angio-Immunoblastic T-Cell Lymphoma	Language was added to Section 4.2.2 to introduce subsections 4.2.2.1, 4.2.2.2, and 4.2.2.3. Sections 4.2.2.1, 4.2.2.2, and 4.2.2.3 were added to discuss enrollment of Cohorts A, B, and C, respectively.	Language added per Health Authority request.
Section 5.2 – Inclusion Criteria, Criterion #10	Criterion #10 contraception language was updated to indicate that appropriate contraception practices should be used for 30 days after the last dose of study drug instead of 180 days. Language for describing the use of hormonal contraception was updated to further specify the kinds of contraception and methods of administration. Specified that these hormonal forms of contraception should be used in combination with a barrier method as HMPL-305 may reduce their effectiveness.	To align with Clinical Trials Facilitation Group (CTFG) requirements related to the acceptable contraceptive methods for males and females of childbearing potential, and the duration of contraception for IMPs with CCI [redacted] based on data in the IMPs IB.
Section 6.2.1.1 – Permanent Discontinuation of Treatment	Revised language for patients that could be discontinued from treatment from "Patients could be discontinued…" to "Patients must be discontinued."	Language updated per Health Authority request.
Section 7.4.3 – Drug-Drug Interactions	Language was updated to include CCI [redacted]. Language was removed suggesting HMPL-306 may CCI [redacted]	Language updated for consistency and clarity.
Section 8.6.7 – Pregnancy	Updated duration of contraception (100 days to 30 days) and pregnancy reporting based on the results of non-clinical studies in the HMPL-306 IB, including genotoxicity, embryofetal development, fertility, and embryonic development.	To align with CTFG requirements related to the acceptable contraceptive methods for males and females of childbearing potential, and the duration of contraception for IMPs with CCI [redacted] based on data in the IMPs IB.

Section Number	Summary of Change	Rationale for Change
Section 8.7 – Duration of Follow-up for Adverse Events	Language was updated to clarify that all pregnancies that occur during study participation should be followed to determine their outcome.	Language was updated for clarity.
Appendix 2 – PK/PD/BIOMARKER/ECG ASSESSMENTS FOR EXPANSION COHORTS	Footnote 4 was added to C2D1 under Blood and Bone Marrow Samples for Gene Mutation Analysis.	This was added for accuracy and clarity.
Appendix 9 – 2015 IWG CRITERIA FOR MEASUREMENT OF TREATMENT RESPONSE IN ADULT MDS/MPN	Footnote was updated to reference the MPN-SAF TSS tool.	Language was updated as the MPN-SAF TSS is a validated tool.

Amendment 2 (30 August 2021)

Section Number	Summary of Change	Rationale for Change
Section 2.3.2 – Benefit Assessment	Added information from currently available published data and a reference to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) treatment guidelines to support the current eligibility criteria for each cohort in this study.	Request by Health Authority
Section 5.1.1.2 – Screening Period	Moved the statement, "If there is dosing on assessment day, all assessment examinations must be completed before study drug administration, except for 12-lead electrocardiogram (ECG), ECHO/MUGA scan, ophthalmologic examination" from this section to Section 6.1.	Request by Health Authority
Section 6.1 – Study Procedures	Moved the statement, "If there is dosing on assessment day, all assessment examinations must be completed before study drug administration, except for 12-lead electrocardiogram (ECG), ECHO/MUGA scan, ophthalmologic examination" from Section 5.1.1.2 to this section.	Request by Health Authority
Section 5.2 – Inclusion Criteria #7	Removed the following language from inclusion criterion #7, "Alternative methods of kidney function assessment may be reviewed with the Sponsor to determine validity and correspondence with other standard methods."	Request by Health Authority

Section Number	Summary of Change	Rationale for Change
Section 5.2 – Exclusion Criteria #17, #18, #19	Added exclusion criteria #17, #18, and #19, respectively: Subjects with a medical condition, physical examination finding, or clinical laboratory finding that, in the Investigator's opinion, contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications. Subjects with a known hypersensitivity to HMPL-306 or to any of its excipients. Subjects with presence of second primary malignant tumors within the last 2 years, with the exception of the following, if medically controlled: basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and carcinoma in situ of the breast.	Request by Health Authority
Section 6.1.10.4 – Blood Chemistry	Revised to add blood glucose as part of the safety monitoring tests.	Request by Health Authority
Section 6.2.1.1 – Permanent Discontinuation of Treatment	Revised language for subjects that would be discontinued from treatment from "may be discontinued" to "could be discontinued" and added reference to Table 9, Table 10, and Table 11.	Request by Health Authority
Section 6.2.2 – Study Stopping Rules	Revised language to clarify that if the study is halted as per Stopping Rules in either the dose escalation part or the dose expansion part, the study will only be restarted after Regulatory Approval as per local regulations.	Request by Health Authority
Section 11.1.1 – Safety Review Committee	In Section 6.2.2, clarified that the provided dose stopping rules common to both dose escalation and dose expansion parts are applicable to individual subjects.	To improve clarity
Appendix 1 – PK/PD/Biomarker/ECG Assessments for Escalation Cohorts Appendix 2 - PK/PD/Biomarker/ECG Assessments for Expansion Cohorts	Revised to include an ECG at screening in order to confirm eligibility.	Request by Health Authority
	Revised to include blood and bone marrow samples for gene mutation analysis at cycle 2 day 1 (C2D1). Updated table title to include PK/PD/Biomarker/ECG assessments for escalation and expansion cohorts	To improve clarity
	Updated footnote 1 to add "Pre-dose bone marrow sample collection should be performed within 24 hours prior to	A 24-hour pre-dose window was added to provide sufficient flexibility in the clinic to

Section Number	Summary of Change	Rationale for Change
	dosing" and to clarify that sample collected 30 minutes before dosing is blood sample	schedule and perform a bone marrow biopsy
Section 5.2 – Inclusion Criteria #2	Updated inclusion criteria #2 to add the following: Part 1 Inclusion Criterion #2c: Subjects who have received prior IDH inhibitor treatment may be enrolled in the escalation phase of the protocol.	To clarify the inclusion criteria that patients who received prior IDH therapy are allowed for Part 1 (dose escalation phase) if they do not have other viable treatment option.
	Part 2 Inclusion Criterion #2d: Subjects must not have progressed on prior IDH treatment unless isoform switching of the IDH mutation has been documented following progression on the prior IDH inhibitor.	To exclude patients with progression on prior IDH therapy in Part 2 unless there is a valid clinical rationale.
Section 5.2 – Inclusion Criteria #9 Section 6.1.10.9 – Pregnancy Test Section 6.1.19 – Follow-up Period	Updated definition of postmenopausal to "at least 12 months of amenorrhea without alternative medical cause."	To align with the Clinical Trial Facilitation Group (CTFG) definition
Section 2.3.1 – Benefit-Risk Assessment, Table 3 Section 5.2 – Inclusion Criteria #10	Updated to clarify that "male subjects with partners of childbearing potential must agree to use a condom" and will be included in the study only if they agree to "use a condom".	To improve clarity
Section 2.2.3 – Supportive Clinical Data	Updated to provide current status of the ongoing phase 1 study NCT04272957 as of 03 August 2021.	To provide updated information
Section 3 – Objectives and Endpoints, Table 4	Updated to include "deaths" within safety primary endpoints for Part 1 and 2 of the study, to be consistent with existing synopsis text.	For correction.
Section 6.1.14 – Efficacy Evaluation	Revised to add imaging as part of the response evaluation Added language for completion of baseline tumor assessment during the screening period Added additional details defining the time points, imaging procedures, and laboratory tests for measurable and evaluable lesions throughout the study. Added details for assessment of myeloid malignancies using blood test, bone marrow aspiration and/or biopsy, and physical examination. Added details for assessment of hematological malignancies that are	To improve clarity

Section Number	Summary of Change	Rationale for Change
	non-myeloid (eg, AITL), using contrast enhanced CT scans (neck, chest, abdomen, and pelvis) and/or PET-CT scans. Enhanced magnetic resonance imaging (MRI) may be used instead of CT scans in patients for whom CT scans are contraindicated.	
	Revised to state that efficacy evaluation of AITL will be performed based on Lugano Classification (Cheson 2014) for Hodgkin and Non-Hodgkin's Lymphoma and not the 2007 IWG criteria.	To provide updated information
Appendix 10 – Lugano Response Criteria for Hodgkin and Non-Hodgkin's Lymphoma	Replaced Appendix 10 with the Lugano Classification (previously 2007 IWG Response).	To provide updated information
Section 6.2.1.1 –.Permanent Discontinuation of Treatment	Updated reference from 2007 IWG Response for patients with AITL to the Lugano Classification.	To provide updated information
Section 8.5 – Causality Assessment	Updated general guidelines for causality assessments.	To align with the Sponsor's protocol template
Section 8.6.9 – Death	Updated guidelines for reporting all deaths that occur during protocol-specified AE reporting period.	To align with the Sponsor's protocol template
Section 8.6.3 – Persistent or Recurrent Adverse Events	Clarified that all recurrent AEs should be recorded in the CRF "as separate events", respectively.	To improve clarity
Section 1.3 – Schedule of Events Table 1 (Dose Escalation) and Table 2 (Dose Expansion)	Added tumor evaluation/imaging at the screening period time points for Part 1 (dose escalation) and Part 2 (dose expansion). Added ECHO/MUGA scan at the cycle 1 day 1 (C1D1) time points for Part 1 (dose escalation) and Part 2 (dose expansion).	To improve clarity
Section 1.3 – Schedule of Events Table 1 (Dose Escalation)	Updated footnote a, to clarify that the analysis of serial blood samples collected from Days 1 to 7 of the PK week will include "other biological markers as defined by the Sponsor."	To improve clarity
Section 4.1.1 – Part 1 (Dose Escalation)	Defined the PK week as "7 days prior to cycle 1 day 1 (C1D1) during which a single dose of HMPL-306 will be administered on day 1 of PK week (day -7 relative to C1D1)." Updated to clarify that the analysis of serial blood samples collected from Days 1 to 7 of the PK week will include "other biological markers as defined by the Sponsor."	To improve clarity

Section Number	Summary of Change	Rationale for Change
Section 5.1.1.2 – Screening Period	Revised definition of screening period to indicate that the period begins at the time of main study consent until the first dose of HMPL-306 (previously, the period was defined to begin at "first screening visit to before the first dose of HMPL-306.")	To improve clarity
Section 10.3 – Informed Consent	Clarified that investigators or designees who obtain the signed ICF must be "qualified by education, training, and experience to comply with GCP and applicable regulatory requirements"	To comply with data privacy regulations/guidance
Section 10.4 – Data Privacy	Added the following clarification: "The investigator and the sponsor or its designee are responsible for ensuring that sensitive information, transfer of data/research samples, and storage of biological material retained for future research is handled in accordance with local requirements."	To comply with data privacy regulations/guidance
Appendix 4 – COVID-19 Risk Assessment	Added a section for guidance on administration of COVID-19 vaccines for patients participating in the study.	To provide updated guidance
Appendix 7 – CCI Inhibitors/Inducers	Several CCI inhibitors/inducers were deleted from Appendix 7 list, and 3 CCI inhibitor were added.	List was revised based on clinical relevance.
Appendix 8 – 2017 European LeukemiaNet Efficacy Criteria for AML	• For treatment response CR and MLFS, changed criteria "No extrathecal lesion" to "No extramedullary lesion". • Revised criterion to include CR_{MRD-} for treatment response SD, as follows: "Fails to meet criteria for CR, CRi, CR_{MRD-}, MLFS, PR, or progressive disease"	To align with the 2017 European LeukemiaNet (ELN) recommendations.
Document History	Updated table to delete unapproved versions from the document history.	This deletion is to improve clarity and align with the Sponsor's approved template since the version numbering is for the Sponsor's document tracking purposes only.
Appendix 13 - Amendment History (New Appendix)	Added summary of Amendment 1 changes to Amendment History	Consistency with Sponsor's process and template

Amendment 1 (20 October 2020)

Section Number	Summary of Change	Rationale for Change
Section 5.2 - Inclusion Criteria #2 Table 4 Objectives and Corresponding Endpoints Section 4.1 - Study Design	Added additional details in the inclusion criteria regarding definition of "advanced" and "locally advanced." Specified that subjects in the dose escalation portion must be refractory to or intolerant of established therapies known to provide clinical benefit. Specified that subjects in the dose expansion portion must have received at least 2 prior lines of therapy for their hematological malignancy. Specified that subjects with MDS must be considered high or very high risk by IPSS-R.	Clarification and addition in response to request by FDA
Section 4.1.1 - Part 1 (Dose Escalation) Table 6 mTPI-2 Decision Table for Dose Selection	Revised text to end the study if DLT is observed in 1 of 3 subjects at the initial dose and included guidance on next steps if this occurs. Also moved this text to Section 6.2.2.2. Updated the mTPI-2 table to include at DLT rate of 20% with an equivalence interval of 15% to 25%.	Request by FDA
Section 8.1.3 - Dose-Limiting Toxicity	Revised the DLT criteria to add the following: • Any Grade ≥4 nonhematologic toxicity • Any Grade ≥3 nonhematologic toxicity unless they resolve within 72 hours of onset • Grade 3 or 4 neutropenia lasting more than 7 days • Confirmed cases of Hy's law For hematologic toxicities, neutropenia or thrombocytopenia that occurs with active leukemia may be excluded.	Request by FDA
Section 6.2.2.2 - Stopping Rules for a Cohort or the Study Table 8 Bayesian Continuous Safety Monitoring Boundaries for n=15 (added)	Added formal rules for the dose expansion portion with Bayesian Continuous Safety Monitoring boundaries specifying that accrual in each respective cohort will be paused if the number of DLTs exceeds the threshold boundary and next steps will be determined based on SRC recommendations. The continuous safety monitoring rules have been revised based on a 20% DLT rate.	Request by FDA
Section 4.1.1 - Part 1 (Dose Escalation) Section 4.1.2 - Part 2 (Dose Expansion) Section 1.1 - Synopsis	Removed language allowing investigator discretion in decisions allowing patients to continue or discontinue treatment based on investigator judgment of whether or not subjects are benefiting from treatment.	Request by FDA
Section 5.2 - Inclusion Criteria #7	Revised inclusion criterion for creatinine clearance to ≥60 mL/min for both dose escalation and dose expansion.	Request by FDA

Section Number	Summary of Change	Rationale for Change
Section 5.2 - Inclusion Criteria #5	Revised text to specify that AITL subjects must have a platelet count ≥20,000/μL for eligibility; however, platelet transfusions are permitted to reach this level.	Request by FDA
Section 7.4.2 - Permitted Therapies	Added a link to the treatment of differentiation syndrome.	Request by FDA
Section 7.4.3 - Drug-Drug Interactions	Added text to specify close and frequent monitoring of adverse events with concomitant use of any medication that is a substrate of CCI and has a narrow therapeutic index.	Request by FDA
Section 7.5.1 Adjustment of Dose within the DLT Assessment Window	Revised to eliminate the option to restart study drug after Grade 4 events. Deleted text allowing subjects to continue treatment if an AE does not meet the DLT criteria or is a Grade 3 or 4 non-DLT.	Request by FDA
Section 7.5.2 - Dose Adjustment Outside the DLT Assessment Window (Including Dose Expansion Part) Table 9 Dose Adjustment for Hematologic Toxicity (added) Table 10 Dose Adjustment for Nonhematologic Toxicity (added)	Revised the guidance for dose adjustment for hematologic and nonhematologic toxicity outside the DLT assessment window with addition of new tables for dose adjustment.	Request by FDA
Section 7.5.3 - Intra-Dose Escalation (deleted section)	Deleted provision for allowing intra-subject dose escalation.	Request by FDA
Section 7.6.1 - Differentiation Syndrome Handling Principles	Added text stating the following: • Hemodynamic monitoring will also be performed with dexamethasone administration. • HMPL-306 will be interrupted in the event of severe pulmonary symptoms or renal dysfunction. Revised condition under which HMPL-306 may resume to specify resumption will occur after symptoms improve to Grade 2 or lower.	Request by FDA
Section 7.6.2 - Handling Principles for Noninfectious Leukocytosis (revised heading)	• Defined noninfectious leukocytosis as WBC $>25\times10^9$/L or an absolute increase in total WBC of $>15 \times 10^9$/L from baseline. • Specified that resuming study drug WBC count should be $<30 \times 10^9$/L in addition to resolution of clinical features of differentiation syndrome.	Request by FDA

Section Number	Summary of Change	Rationale for Change
Section 7.6.2 - Handling Principles for Noninfectious Leukocytosis (revised heading)	Revised hydroxyurea oral therapy instructions to align with institutional standards.	Clarification
Section 7.5.3 - Dose Adjustment for QT Interval Prolongation (section added) Table 11 Dose Adjustment for QT Interval Prolongation (table added)	Added guidance for dose adjustment for QT interval prolongation.	Request by FDA
Section 6.1.10.4 - Blood Chemistry	Added uric acid to list of blood chemistry tests.	Request by FDA
Section 6.1.9 - Ophthalmologic Examination	Added OCT to list of ophthalmic examinations. Specified dose adjustments required if RPE detachment is noted.	Request by FDA
Appendix 1 PK/PD/Biomarker/ECG Assessments for Escalation Cohorts Appendix 2 PK/PD/Biomarker/ECG Assessments for Expansion Cohorts Section 4.2.3 - Rationale for Biomarker Testing	Added mutational analysis for CCI .	Request by FDA
Section 6.2.1.1 - Permanent Discontinuation of Treatment	Revised conditions for permanent discontinuation of treatment to specify that all patients may receive a maximum of 6 treatment cycles. Defined conditions under which patients may not receive the maximum number of treatment cycles.	Request by FDA
Section 7.5.2 - Dose Adjustment Outside the DLT Assessment Window (Including Dose Expansion Part)	Specified that dose adjustments are to be made for any adverse event deemed at least possibly related to HMPL-306.	Request by FDA
Section 7.5.3 - Dose Adjustment for QT Interval Prolongation Table 11 Dose Adjustment for QT Interval Prolongation	Modified the dose adjustment for QTc prolongation based on the USPI for ivosidenib.	Request by FDA
Section 4.2.2 - Rationale for Study Population Selection	Added text and references to clarify rationale for use of HMPL-306 for treatment of MDS, MPN, and AITL.	Suggestion by FDA

Section Number	Summary of Change	Rationale for Change
Table 3 Summary of Potential Risks of HMPL-306	Changed frequency of WBC monitoring from weekly in Cycle 2 to every other week in Cycle 2. Removed text "medication" from "patient medication guide."	To align with the schedule of events To align with operational conduct of the trial
Appendix 4 COVID-19 Risk Assessment	Remove text "#5."	Correct discrepancy with exclusion criterion #
Section 4.1 - Study Design	Removed specification that patients need to be refractory to 2 prior lines of therapy to qualify for enrollment.	This text only applies to the dose expansion.

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