HUTCHMED

A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-689 in Patients with Relapsed or Refractory Lymphoma

Protocol number:	2018-689-00US1
Amendment number:	5
Investigational product:	HMPL-689
Study phase:	1
Sponsor:	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China 201203
IND:	CCI [redacted]
EudraCT:	2018-004808-19
ClinicalTrials.gov ID:	NCT03786926
Issue Date:	08 December 2022

STATEMENT OF COMPLIANCE

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

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

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

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

SPONSOR'S APPROVAL

Title	A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-689 in Patients with Relapsed or Refractory Lymphoma
Protocol Number	2018-689-00US1
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: [last name, first name] PPD , MD	**Title:** PPD HUTCHMED International Corp.
Signature: *See appended signature page*	**Date:** [DD-Mon-YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2018-689-00US1 and agree to the following:

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

Name [Print last name, first name]	**Title** [Title at institution]	**Institution** [Address]
Signature		**Date** [DD Mon YYYY]

DOCUMENT HISTORY

Amendment	Issue Date
Original Protocol	13 Nov 2018
1	04 Aug 2020
2	20 Jan 2021
3	04 June 2021
4	28 March 2022

AMENDMENT SUMMARY

This Protocol 2018-689-00US1 Amendment 5 replaces Protocol 2018-689-00US1 Amendment 4. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary purpose of Amendment 5 is to provide notification that further enrollment to this study has been halted based upon the strategic evaluation of the clinical development of HMPL-689 in the United States, Europe, and Australia with HUTCHMED as the study Sponsor. This change is not based on any concern for patient safety or efficacy relative to HMPL-689 treatment. Currently enrolled patients who are deriving clinical benefit from treatment with HMPL-689 may continue to participate in the study as per the protocol. There is no planned interruption in the supply of HMPL-689 to clinical trial sites with active patients. The changes made in this amendment are described in the table below. Editorial and formatting changes are not included in this summary.

Details of prior amendments are summarized in Appendix 17.

Section Number	Summary of Change	Rationale for Change
Cover Page, Sponsor's Approval, Document History, Header, and Footer	Administrative updates made to reflect Amendment 5.	The administrative updates were made to reflect Amendment 5.
Synopsis, Section 4.1.2 – Dose Expansion Stage (Stage 2), and Section 5.1 – Patients	Language was added to indicate that consenting to the study was halted as of CCI Currently enrolled patients deriving clinical benefit from treatment may continue to participate in the study.	This new language confirms that consenting to the study was halted on CCI This language also confirms this change is not based on any patient safety or efficacy concerns, and to ensure patients deriving clinical benefit from study treatment may continue treatment.
Synopsis and Section 4.1.5 – Tumor Assessment and Response Evaluation	Language indicating patients discontinuing HMPL-689 due to other reasons other than disease progression will continue tumor assessments was removed. Language and Section heading related to blinded independent central review of baseline and subsequent tumor imaging was removed.	This language was removed as it no longer applies as of implementation of this protocol amendment.
Synopsis and Section 7.1 – Determination of Sample Size	Language was added to confirm the total expected enrollment is approximately CCI patients and approximately CCI patients are expected to enroll in the Dose Expansion Stage (Stage 2). Language associated with the change in expected enrollment was removed or updated for clarity.	The new language confirms the expected enrollment upon completion of enrollment upon implementation of this protocol amendment.
Synopsis, Section 3 – Objectives and Endpoints, Section 4.1.7 – Extended	Any language, headings, tables, and analyses related to assessments, objectives, and endpoints that fall	This language was updated or removed to clarify what assessments, objectives, and

Section Number	Summary of Change	Rationale for Change
Progression-Free Survival Follow-Up Period, Section 5.7 – Study Assessments, Section 5.8.2 – Extended Progression Free Survival Follow-up, Section 5.9 - Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Assessment Methods, Section 7 – Statistical Analysis, and Appendix 1, 2, 3, and 4.	outside of the scope of the necessary assessments for the safety review committee (SRC) to monitor the benefit/risk of patients remaining on trial were updated or removed.	endpoints are still relevant upon implementation of this protocol amendment.
Synopsis and Section 5.7.2 – Informed Consent Forms and Screening Log	Language regarding rescreening was updated to indicate that patients will not be rescreened upon implementation of Protocol Amendment 5.	This language was added to clarify that rescreening will no longer be permitted upon implementation of this protocol amendment.

EMERGENCY CONTACT

Under urgent circumstances, please contact the sponsor's medical monitor or the designee.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AO	Aldehyde oxidase
aPTT	Activated partial thromboplastin time
AR	Accumulation ratio based on AUC
AST	Aspartate transaminase
AT	Aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve over the last 24-h dosing interval
AUC_{0-t}	Area under the concentration-time curve in a selected time interval
BCRP	Breast-cancer resistance protein
BID	Twice daily
B-NHL	B-cell non-Hodgkin lymphoma
BTK	Bruton's tyrosine kinase
CBCL	Cutaneous B-Cell Lymphoma
CBR	Clinical benefit rate
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine clearance (estimated per Cockcroft-Gault)
CRF	Case report form
CRi	Complete response with incomplete bone marrow recovery
CRO	Contract research organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOT	End of treatment
EUA	Emergency Use Authorized
FACS	Fluorescence activated cell sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FMO	Flavin-containing monooxygenase
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HL	Hodgkin lymphoma
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Concentration of a drug required for 50% inhibition in vitro
ICF	Informed consent form
ICH	International Conference for Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
iNHL	Indolent non-Hodgkin lymphoma
INR	International normalized ratio
IP	Investigational product
IPI	International Prognostic Index
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISSWM	International prognostic scoring system for Waldenström's macroglobulinemia
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWWM	International Workshops on Waldenström's macroglobulinemia
KM	Kaplan-Meier
LDH	Lactate dehydrogenase

Abbreviation	Definition
LOAEL	Low-observed-adverse-effect level
LPL/WM	Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	Modified toxicity probability interval scheme-2
MUGA	Multigated acquisition scan
MZL	Marginal zone lymphoma
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
nPR	Nodular partial response
NYHA	New York Heart Association
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PGx	Pharmacogenetic
PI3K	Phosphatidylinositol 3-kinase
PI3Kδ	Phosphatidylinositol 3-kinase p110 δ isoform
PI3Kγ	Phosphatidylinositol 3-kinase γ isoform
PJP	*Pneumocystis jiroveci* pneumonia (formerly called *Pneumocystis carinii* pneumonia [PCP])
PKAP	Pharmacokinetic analysis plan
PKAS	Pharmacokinetics analysis set
PK	Pharmacokinetic(s)
PPB	Plasma protein binding
PR	Partial response
PR-L	Partial response with lymphocytosis
PS	Performance status
PT	Prothrombin time
PTCL	Peripheral T-cell lymphoma
QD	Once daily (from the Latin quaque die)
QTc	Corrected QT interval

Abbreviation	Definition
QTcF	Corrected QT interval by Fredericia
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RR	The time elapsed between 2 successive R-waves of the QRS signal on the ECG
SAE	Serious adverse event
SD	Stable disease
SDV	Source data verification
SLL	Small lymphocytic lymphoma
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SRC	Safety review committee
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum plasma concentration
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
USP	United States Pharmacopeia
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

1 PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol Number</td><td>2018-689-00US1</td></tr>
<tr><td>Title</td><td>A Phase 1, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-689 in Patients with Relapsed or Refractory Lymphoma</td></tr>
<tr><td>Study Phase</td><td>Phase 1</td></tr>
<tr><td>Sponsor</td><td>HUTCHMED Limited</td></tr>
<tr><td>Investigational product</td><td>HMPL-689</td></tr>
<tr><td>Study Status as of Protocol Amendment 5</td><td>CCI [redacted]</td></tr>
<tr><td>Planned Enrollment</td><td>CCI [redacted]</td></tr>
<tr><td>Study Duration</td><td>Approximately 48 months</td></tr>
<tr><td>Objectives and Endpoints</td><td>
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<tr><th>Tier</th><th>Objectives</th><th>Endpoints</th></tr>
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• Safety (including but not limited to TEAEs, treatment-related adverse events [TRAEs], SAEs, treatment-related SAEs [TRSAEs], and lab abnormalities)</td></tr>
<tr><td>Primary – Dose Expansion</td><td>To further evaluate safety and tolerability of HMPL-689 at MTD in patients with relapsed, refractory, or resistant lymphoma</td><td>• Safety, including TEAEs and TRAEs</td></tr>
<tr><td rowspan="2">Secondary</td><td>To assess preliminary efficacy of HMPL689 in patients with relapsed, refractory, or resistant lymphoma overall and by lymphoma sub-types as assessed by investigator</td><td>• ORR
• TTR
• DoR
• CBR
• PFS</td></tr>
<tr><td>To characterize PK parameters of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma at both dose escalation and dose expansion stages</td><td>• Concentration-time profiles and PK parameters after single dose and at steady state</td></tr>
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		To evaluate the effect of HMPL-689 on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals	• QTc interval and HMPL-689 concentration

Study Design

This is a phase 1, open-label, multicenter study of HMPL-689 administered orally to patients with relapsed, refractory, or resistant lymphoma.

This study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). Both Stage 1 and Stage 2 include the following periods: screening period, treatment period, safety follow-up period, and extended progression-free survival (PFS) follow-up period.

Dose Escalation Stage (Stage 1)

Dose escalation will be performed according to a modified toxicity probability interval scheme-2 (mTPI-2), and HMPL-689 will be titrated using a modified Fibonacci design allowing dose increments in subsequent dose levels. The dose escalation is planned at 5 mg once daily (QD), 10 mg QD, 15 mg QD, 20 mg QD, 25 mg QD, 30 mg QD, 35 mg QD, 40 mg QD, 45 mg QD, and 50 mg QD (dose levels 1–10).

Design Characteristics of mTPI-2

- The maximum sample size for this stage will be determined by the sponsor and investigators based on the accumulated data and the mTPI-2 design. The maximum recommended sample size under mTPI-2 design is $k \times (d + 1)$, where k denotes the cohort size and d denotes the number of doses. In this study, the minimum cohort size is 3.
- The equivalence interval of toxicity probability for the MTD is (25%, 35%). This interval is derived based on the following parameters:
  - The target probability of toxicity (p_T) is set to 30%.
  - Both epsilon 1 (ε1) and epsilon 2 (ε2) are set to 0.05.
- This stage will end when any of the following criteria are met:
  - The dose level 1 demonstrates an excessive toxicity, i.e., 3 dose-limiting toxicities (DLTs) are observed out of the first 3 patients at dose level 1.
  - The maximum sample size is reached.
  - The MTD and/or recommended phase 2 dose (RP2D) is confirmed.

Dose Escalation Rules

- The starting dose is dose level 1: 5 mg QD.
- If a lower dose is needed upon results from dose level 1, dose level -1 will be explored.
- Three patients will be enrolled for the initial cohort (dose level 1).
- At the end of the DLT assessment window for a dose level, decision on the dose of the next dose level will follow the mTPI-2 rule, which leads to enrollment of another 3 patients at the next step.
- In the event that the first two patients within a given dose level experience DLT events but the third patient has not yet begun protocol treatment, the third patient should receive a lower dose per the mTPI-2 algorithm.

At the end of Stage 1, the MTD will be determined based on the number of patients treated and the number of experienced DLT at each dose level.

Definition of Dose Limiting Toxicity

Dose limiting toxicities are defined as the occurrence of any of the following treatment -emergent adverse events (TEAE) during the DLT assessment window (Cycle 1, Day 1 through Cycle 1, Day 28), unless equivocally due to underlying malignancy or an extraneous cause:

a. Nonhematologic toxicity: All nonhematologic TEAEs of Grade 3 or greater with the exception of:
    i. Grade 3 nausea or vomiting that can be controlled by supportive therapy
b. Hematologic toxicity:
    i. Grade 4 neutropenia lasting for more than 5 days
    ii. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding event or requiring platelet transfusion
    iii. Grade ≥3 febrile neutropenia (defined as ANC <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)
    iv. Grade 4 anemia not explained by underlying disease
c. Any TEAE requiring a dose delay of ≥15 days
d. Any case of Hy's Law

Dose Limiting Toxicity Assessment Window

For all patients in Stage 1, DLTs will be assessed during a DLT assessment window of 28 days (i.e., from Cycle 1, Day 1 [the day of the first administration of treatment] through Cycle 1, Day 28).

Definition of DLT-Evaluable Patient

For decisions on dose escalation, each dose cohort shall present the protocol-required number of DLT-evaluable patients. A patient is DLT evaluable if he/she:

- has received at least 75% of the assigned dose of study treatment during the DLT assessment window (ie, Days 1 to 28);

  or

- has not completed the DLT assessment period due to a DLT.

Patients who are not DLT evaluable in a dose cohort will be replaced to guarantee the protocol-required number of DLT-evaluable patients for each dose cohort.

Dosing Beyond Cycle 1

Patients who complete the DLT assessment window and are deemed by the investigator to be benefiting from HMPL-689 treatment may continue with HMPL-689 treatment until disease progression, death, intolerable toxicity, investigator's discretion that the patient can no longer benefit from the study treatment, withdrawal of consent, or the end of study, whichever occurs first.

During the study treatment period, including the DLT assessment window, patients will not be allowed to make up missed doses.

Definition of MTD

The MTD is the dose with a posterior toxicity probability closest to the target toxicity probability ***pT***, i.e., closest to 30%. In case all doses have toxicity probabilities greater than (***pT*** + ε2), i.e., 35%, no dose will be considered as the MTD.

Posterior toxicity probability at each dose level will be estimated based on beta posterior distribution and application of pooled adjacent violator's algorithm.

Definition of Recommended Phase 2 Dose

The decision regarding the RP2D will take the following into consideration:

- MTD, if reached;
- Pharmacokinetics with or without associated safety and preliminary efficacy findings.

These criteria constitute the basis for RP2D determination. Both the sponsor and the safety review committee (SRC) must agree on the RP2D.

Dose Expansion Stage (Stage 2)

The safety, tolerability, PK, and preliminary efficacy of HMPL-689 at MTD/RP2D will be further evaluated in patients with relapsed, refractory, or resistant non-Hodgkin lymphoma [NHL].

Amendment 4:

CCI

[redacted]

Amendment 5:

CCI

[redacted]

Safety Monitoring

Safety monitoring and dose escalation determination will be conducted by an SRC, which consists of the sponsor's medical monitor, drug safety lead, PK scientists, and the sites' Principal Investigators (PIs) or delegate, as applicable. Safety will be monitored continuously throughout the conduct of this study by the SRC. There will be periodic reviews of emerging data on safety, PK, drug exposure, target engagement, pharmacodynamics, and clinical response to determine continuation (or otherwise) of an individual participant, cohort arm, or entire expansion stage.

The SRC for dose escalation stage may extend to the expansion stage or a new one may replace this SRC, with the same mandate.

Lifestyle Management

Full assessment of extensive non-clinical studies indicated HMPL-689 has no phototoxic effects. Furthermore, experience from ongoing clinical studies in China and Australia also confirm that this study drug lacks any phototoxic effect. Nonetheless, patients enrolled in this study are advised to avoid unnecessary long-term and direct exposure to sunlight or any other source of ultraviolet (UV) light during their participation in the study and until 30 days after the last dose of study drug. Patients are also encouraged to wear sunglasses and apply sunscreen products with protective coefficient of at least SPF 15 whenever possible.

	Tumor Assessment and Response Evaluation Tumor assessment and response evaluation will be performed using the International Workshop on CLL guideline for patients with CLL, the consensus of International Workshops on WM (IWWM-7 consensus) for patients with LPL/WM, and the Lugano response criteria for patients with other lymphomas. Tumor response will be assessed by investigators according to the response criteria for the respective disease subtypes every 8 weeks (±7 days) for the first 24 weeks and every 12 weeks (±7 days) thereafter. Patients who discontinue HMPL-689 treatment due to reasons other than disease progression will continue tumor assessment according to the previous tumor assessment schedule until disease progression, death, end of the study, or start of new antineoplastic therapy, whichever is earlier. Upon implementation of Protocol Amendment 5, this assessment will no longer be required. Determination of disease progression will occur locally by the investigator in accordance with respective disease criteria. **Safety Follow-Up Period** The safety of all enrolled patients will be closely monitored after informed consent has been obtained until 30 days after the last dose of treatment or the initiation of new antineoplastic therapy, whichever comes earlier. After the safety follow-up period, investigators shall only report the follow-up of unresolved serious adverse events (SAEs) that are related to prior study treatment of HMPL-689. All adverse events (AEs) will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. **Extended PFS Follow-Up Period** Patients who discontinue HMPL-689 treatment due to reasons other than disease progression will enter the extended PFS follow-up period. During this period, tumor assessment will be conducted quarterly until disease progression, death, the end of the study, or the initiation of new antineoplastic therapy, whichever comes earlier. Upon implementation of Protocol Amendment 5, this assessment will no longer be required. **End of Study** The end of the study is defined as 18 months after the last patient has been enrolled in the study or all patients have discontinued the study treatment, whichever comes earlier.
Study Treatment	HMPL-689 is in capsule formulation for daily oral administration.
CCI [redacted]	CCI [redacted]

Criteria for Inclusion	Patients must meet the following criteria to be eligible for study entry: 1. Signed informed consent form (ICF); 2. Age ≥18 years; 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 4. Histologically confirmed NHL of the following sub-types CLL/SLL, FL (grade 1-3a), MCL, MZL, LPL/WM, PTCL or CBCL; • Patients with CLL/SLL, FL (grade 1-3a), MCL and LPL/WM must have received at least 2 prior lines of systemic therapy. • Patients with MZL must have received at least 1 prior line of systemic therapy that includes an anti-CD20 monoclonal antibody agent. • Patients with PTCL and CBCL must have received at least 1 prior line of systemic therapy. 5. Patients with relapsed, refractory, or resistant NHL, as defined below: • Refractory to any prior regimen, defined as no response (complete response or partial response) to previous therapies, or progression within 6 months of completion of the last dose of prior therapy. • Those who can no longer tolerate/withstand cytotoxic chemotherapy and/or available standard of treatment/care (SoT/SoC), where safety profile and risks of toxicity of other treatment options far outweigh any possible clinical benefit. • Those with no curative SoT or no reasonable access to available treatments, in particular, those who will benefit from this class of compound, in the opinion of the attending investigator. 6. In the dose expansion stage, patients must have measurable disease for an objective response assessment, except for patients with CLL and WM/LPL. NOTE: Measurable disease with FL, MCL, MZL, PTCL, CBCL, or SLL is defined as at least 1 bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by computerized tomography [CT] scan). 7. Expected survival of more than 24 weeks as determined by the principal investigator. 8. Patients with prior treatment with any PI3Kδ inhibitors are eligible for dose escalation. However, during dose expansion, only patients that discontinued PI3Kδ inhibitor for reasons other than disease progression are eligible. 9. Male patients must agree to use a condom and female patients of childbearing potential must agree to use highly effective contraceptive measures that result in a low failure rate (<1% per year) when used consistently and correctly, from the screening period, through the entire study period, and for 30 days after the last dose of study drug. These highly effective contraceptive measures, as defined by the Clinical Trials Facilitation Group (CTFG)*, include combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device or intrauterine hormone-releasing system, bilateral tubal occlusion, a vasectomized partner, or sexual abstinence if in the preferred and usual lifestyle of the patient. These same criteria are applicable to partners of patients involved in this clinical study if that partner is of childbearing potential. Postmenopausal females (no menses for 12 months

	without an alternative medical cause) and surgically sterilized females are exempt from this criterion. *Note: In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.
Criteria for Exclusion	Patients who meet any of the following criteria will be excluded from study entry: 1. Patients with primary central nervous system (CNS) lymphoma; 2. Any of the following laboratory abnormalities: • Absolute neutrophil count $<1.0 \times 10^9$/L • Hemoglobin <80 g/L • Platelets $< 50 \times 10^9$/L NOTE: In the dose expansion stage, patients with cell counts below the thresholds listed above may be considered eligible if, in the investigator's opinion, the reason is bone marrow infiltration. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval by the sponsor will a patient with cell counts below the thresholds be enrolled in the study. NOTE: In the dose expansion stage, patients with ≤G2 neutropenia per CTCAE version 5.0 and/or thrombocytopenia and with confirmed bone marrow infiltration are eligible. 3. Inadequate organ function, defined by the following: • Total bilirubin >1.5 times the upper limit of normal (× ULN), with the following exception: – Patients with known Gilbert's disease who have serum total and direct bilirubin level ≤2.5 × ULN and normal aspartate transaminase (AST) and alanine transaminase (ALT) can be enrolled. • AST or ALT >2.5 × ULN, with the following exception: – In the dose expansion stage, patients with documented disease infiltration of the liver may have AST and ALT levels ≤5 × ULN. • Estimated creatinine clearance (CrCl) per Cockcroft-Gault – Dose escalation stage of trial (Stage 1) – CrCl <40 mL/min – Dose expansion stage of trial (Stage 2) – CrCl <30 mL/min 4. International normalized ratio (INR) >1.5 × ULN, activated partial thromboplastin time >1.5 × ULN or prothrombin time >1.5 × ULN; • Patients requiring anticoagulation therapy but with a stable INR within the recommended range according to the local guideline are eligible. NOTE: Patients may be considered for the study if kidney function is impaired but this impairment is believed to be a result of the patient's underlying disease. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval by the sponsor will a patient with impaired kidney function due to underlying disease be enrolled in the study.

	5. Serum amylase or lipase >ULN at screening or known medical history of serum amylase or lipase >ULN; NOTE: Patients with known medical history of serum amylase or lipase >ULN are eligible in the dose expansion stage. 6. Patients with presence of second primary malignant tumors within the last 2 years, with the exception of: • Basal cell carcinoma of the skin • Squamous cell carcinoma of the skin • Carcinoma in situ of the cervix • Carcinoma in situ of the breast 7. Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with human immunodeficiency virus (HIV), cytomegalovirus (CMV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Active infection is defined as one requiring treatment with antiviral therapy, presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody), or CMV or HCV antibody. • Patients who are positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV deoxyribonucleic acid (DNA). These patients will require HBV DNA PCR monitoring, as per local standards. • Patients who are positive for CMV or HCV serology are eligible only if testing for CMV DNA or HCV RNA is negative. 8. Any anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, vaccine, or radiotherapy within 3 weeks prior to initiation of study treatment; 9. Any granulocyte colony-stimulating factor treatment/blood transfusion within 7 days before the screening hematology test; 10. Any steroid therapy or approved targeted small molecule agents for anti-neoplastic intent within 7 days or approximately 5 half-lives, whichever is longer, prior to initiation of study treatment; 11. Prior use of any drug that is a strong inducer of cytochrome P450(CYP)3A4 or strong inhibitor of CYP3A4 within 2 weeks prior to initiation of study treatment (3 weeks for St John's Wort); 12. Prior autologous transplant within 6 months prior to initiation of study treatment; 13. Prior allogeneic stem cell transplant within 6 months prior to initiation of study treatment or with any evidence of active graft versus host disease or requirement for immunosuppressants within 21 days prior to initiation of study treatment; 14. Clinically significant active infection (e.g., pneumonia) or interstitial lung diseases; (including drug induced pneumonitis); 15. Major surgical procedure within 4 weeks prior to initiation of study treatment; 16. Treatment within a clinical study of an investigational agent or using an investigational device within 30 days prior to initiation of the current study treatment; 17. Adverse events from prior anti-neoplastic therapy that have not resolved to Grade ≤1, except for alopecia;

	18. Pregnant (positive serum beta human chorionic gonadotropin [β-HCG] or urine test) or lactating women; 19. New York Heart Association (NYHA) Class II or greater congestive heart failure; 20. Congenital long QT syndrome or QTc >470 msec; 21. Currently use medication known to cause QT prolongation or torsades de pointes (see full list at http:// www.crediblemeds.org); 22. History of myocardial infarction or unstable angina within 6 months prior to initiation of study treatment; 23. History of stroke or transient ischemic attack within 6 months prior to initiation of study treatment; 24. Inability to take oral medication, prior surgical procedures affecting absorption, or active peptic ulcer disease; 25. History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis); 26. Patients with ongoing chronic gastrointestinal diseases; 27. Legally protected adults; 28. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk of treatment complications.

Statistical Methods

Determination of Sample Size

CCI [redacted]. In general, the maximum sample size in the dose escalation stage will be determined by sponsor and investigator based on the accumulated safety data and the mTPI-2 design. CCI [redacted]. Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than DLT or receive less than 75% of assigned study medication during DLT assessment window will be replaced. This may result in actual enrollment exceeding planned enrollment.

Stage 1: Dose Escalation Stage

The maximum sample size for this stage will be determined by the sponsor and investigator, based on the accumulated safety data and the mTPI-2 design. The maximum sample size under mTPI-2 design is $k \times (d + 1)$, where k denotes the cohort size and d denotes the number of doses. The cohort size in this study is minimum 3 patients per cohort. To ensure that the highest dose (if needed) is reached per the mTPI-2 design and the availability of additional cohorts, it is estimated that approximately CCI [redacted] patients will be needed in this portion of the study.

Stage 2: Dose Expansion Stage

Amendment 4:

CCI [redacted]

Amendment 5:

CCI

Statistical Analysis:

Data will be summarized by dose level, subtype of malignancy and for overall as appropriate. In Stage 2 of the protocol, each lymphoma subtype cohort will be analyzed independently and in aggregate. Continuous assessments will be summarized in descriptive statistics by the number of patients (n), mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include the number and percentage of patients for each category.

Safety Analysis:

Exposure to study drug will be summarized and listed.

Dose limiting toxicities will be listed. The incidence of TEAEs, SAEs, AEs of special interest, TEAEs leading to dose adjustment, or treatment discontinuation will be presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term, by relationship to study drug and by toxicity grade for each dose level. Shift of laboratory test results will be summarized according to the NCI CTCAE grade or normal ranges if not gradable. Descriptive statistics for vital signs and 12-ECG parameters will be presented by dose level and visit. Physical examination findings will be listed.

Pharmacokinetic Analysis:

Non-compartmental model and population model-based analyses will be performed for plasma concentration data. Individual and mean plasma concentrations of HMPL-689 versus time data will be tabulated and presented. Descriptive analysis (n, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [%CV]) for all of the relevant PK parameters of HMPL-689 will be presented. Individual and mean HMPL-689 concentrations will be plotted by dose level.

Efficacy Analysis:

The best percent change from baseline (%) in the target lesion, ORR, CBR and 95% CI based on Clopper-Pearson method will be presented by dose level for each type of malignancy. The PFS, TTR, and DoR will be estimated with Kaplan-Meier (KM) method if data permits, and the corresponding KM curve will be plotted for each type of malignancy.

Tumor assessment in different types of malignancies will be evaluated according to specified guidelines/criteria:

1. CLL: the modified International Workshop on CLL guideline
2. LPL/WM: consensus of international workshops on WM (IWWM-7 consensus)
3. Other lymphomas: Lugano Response Criteria for Hodgkin and NHL

2 INTRODUCTION

Lymphoma is a group of blood cell tumors that develop from lymphatic cells. The two main categories of lymphomas are Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL). Hodgkin lymphomas account for 10% of all lymphomas and less than 1% of all cancers diagnosed in the United States (US) yearly. Approximately 8,500 new patients will be diagnosed with HL and 1,050 will die of the disease in the United States in 2018 (NCI 2018). Non-Hodgkin lymphomas are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer (NK) cells. In the US, B-cell lymphomas account for 80% to 85% of lymphomas and range from slow-growing indolent and incurable diseases (such as follicular lymphoma [FL] or chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]) to more aggressive lymphomas (such as diffuse large B-cell lymphoma [DLBCL]). Mantle cell lymphoma (MCL) is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes owing to incurability of disease (Teodorovic 1995). Diffuse large B-cell lymphoma has the highest incidence of NHL accounting for approximately 30-40% of all new patients, whereas FL and MCL account for approximately 20-25% and 6-10% of other lymphomas, respectively. B-cell CLL is the most common chronic leukemia in adults in western countries and been classified as one of mature B-cell malignancy. Lymphoplasmacytic lymphoma/ Waldenström's macroglobulinemia (LPL/WM) is another indolent B-cell lymphoma that occurs in less than 2% of patients with NHL. A unique characteristic of the disease is that the B-cells produce excess amounts of immunoglobulin protein (IgM), thickening the blood, and infiltration of bone marrow with lymphoplasmacytic cells. Approximately 74,680 new patients will be diagnosed with NHL and 19,910 will die of the disease in the US in 2018 (NCI 2018).

2.1 Current Therapies and Unmet Medical Need

Globally, there were 465,000 incident cases of NHLs and 226,000 deaths in 2013. Non-Hodgkin lymphomas caused 6.4 million disability-adjusted life years (DALYs) in 2013, with 71% occurring in developing countries and 29% occurring in developed countries (Fitzmaurice 2015). Non-Hodgkin lymphoma ranked the 8th for cancer incidence and 11th for cancer death in 2013. In developed countries, it ranked 7th for incidence and 9th for mortality, and in developing countries it ranked 11th for both incidence and mortality (Vanhaesebroeck 2012). Non-Hodgkin lymphoma is the seventh leading site of new cancer cases among men and women, accounting for 4% of new cancer cases and 3% of cancer-related deaths (Vanhaesebroeck 2010).

The mainstay of treatment for NHL is anti-CD20 antibodies (including rituximab, ofatumumab, and obinutuzumab [GA101]) and chemotherapies such as alkylating agents, anthracyclines, antimitotic agents, or purine analogues either alone or in combination settings. Although the current treatments for indolent NHL (iNHL) are initially effective in inducing responses in most patients, they are not curative and show decreasing efficacy with repeated administrations. The majority of patients are elderly, and not all patients can tolerate aggressive chemotherapy. Patients with high-risk cytogenetics have inferior responses to standard treatments or shorter duration of response (DoR). In addition, chemotherapy-based regimens are associated with long-term toxic effects, including cumulative myelosuppression, neuropathy, cardiac toxicity, and secondary cancers (Lunning 2012, Gribben 2007, Leonard 2008).

Investigation of the genetic abnormalities that underlie NHL is providing targets for the development of innovative treatments. Several drugs have been approved for the treatment of

different types of relapsed NHL, most notably the B-cell signaling pathway kinase inhibitors ibrutinib (Imbruvica®), idelalisib (Zydelig®), copanlisib (Aliqopa®) and acalabrutinib (Calquence®). However, these patients are rarely cured with these new treatments, and they still need options after the progression or relapse from the currently available treatment. Furthermore, a good candidate with good single agent tolerability and efficacy to combine with the current standard of care to provide better efficacy in the front line is also desired.

2.2 Background on HMPL-689

2.2.1 Preclinical Pharmacology

HMPL-689 is a novel, highly potent and selective phosphatidylinositol 3-kinase kinase p110 δ isoform (PI3Kδ) inhibitor with an IC_{50} of 0.0008 μM in a PI3Kδ kinase enzymatic assay. HMPL-689 displayed excellent selectivity against a Kinase Profiler™ panel of 323 kinases as well as in a CEREP panel of 80 pharmacological targets in vitro. At the cellular level, HMPL-689 effectively inhibited the phosphorylation of its downstream signaling molecule AKT in Ramos (human Burkitt's lymphoma) cells upon anti-IgM stimulation with an IC_{50} value of 0.001 μM. HMPL-689 significantly inhibited cell viability and induced apoptosis of SU-DHL-6 (human B-cell lymphoma) cells. In addition, HMPL-689 inhibited the survival of multiple B-cell NHL lines, such as Pfeiffer, RL and REC-1 etc. Furthermore, HMPL-689 showed potent inhibitory activity against anti-IgM stimulated survival of B-cells derived from CLL patients, along with potent inhibition of release of chemokines CCL3 and CCL4, which are involved in B-cell homing, from those primary cells. At whole blood level, HMPL-689 significantly inhibited anti-IgD dependent B-cell activation (CD86 expression) in rat whole blood with an IC_{50} of 0.004 μM and anti-IgE induced basophils activation (CD63 expression) in human whole blood with an IC_{50} of 0.003 μM.

The ability of HMPL-689 to inhibit the activation of B-cells in vivo was evaluated in rat using an ex vivo assay. Blood samples from the rats were collected after oral administration of HMPL-689 at various doses and different time points. The samples were stimulated with anti-IgD overnight and B-cell activation in rat whole blood was examined. The data showed that HMPL-689 inhibited expression of CD86 on the surface of B-cells in rat whole blood in a dose- and time- dependent manner, with excellent correlation to the drug exposure. The exposure (470 h•ng/mL) at the potential efficacy dose was achieved through concentration values that exceeded the EC_{90} of B-cell activation from *in vivo* target inhibition study for 24 hours.

2.2.2 Preclinical Pharmacokinetics

The pharmacokinetic (PK) properties, metabolic profile, and potential for drug-drug interaction (DDI) of HMPL-689 were evaluated both in vitro and in vivo. HMPL-689 was found to have high intrinsic membrane permeability and good oral absorption in mice, rats, dogs and monkeys. HMPL-689 could extensively distribute into most tissue (liver, muscle, stomach, fat, small intestine etc.) with higher exposure than plasma after oral administration in rats. HMPL-689 was able to penetrate the blood-testis barrier and blood brain barrier, but the exposure in testis, spinal cord, and brain were lower than in plasma (exposure ratio between 0.1 to 1). The volume of distribution at steady-state (V_{ss}) was similar across different preclinical species (rat: 1.7 L/kg; mouse: 1.9 L/kg; dog: 2.4 L/kg; monkey: 1.5 L/kg). The plasma protein binding (PPB) rates of HMPL-689 were concentration-independent and remained constant (around 90%) at the test concentration range of 0.1-20 μM among all tested species (mouse, rat, dog, monkey, and human).

In vivo clearance was found to be low in mouse, rat, and monkey and to be medium in dog. The metabolic stability of HMPL-689 in human liver microsomes was better than in preclinical species, which suggest low in vivo clearance in human. A total of 20 metabolites, including phase 1 metabolites (M2, M4-M20) and glutathione conjugation products after mono-oxidation (M1 and M3), were detected in the incubation systems of liver microsomes and S9 fractions from different species.

Metabolites in liver microsomal system of rat, dog, and monkey could cover most metabolites generated in that of human. The relative level of metabolites in monkey was much higher than in human, especially M11. The terminal half-life ($t_{½}$) values in all species were around 2-3 hours after intravenous administration. HMPL-689 could be metabolized by several metabolic enzymes including cytochrome P450 (CYP) enzymes (CYP3A4/5, CYP2C8, CYP2D6, CYP2C9, CYP2C19, and CYP2E1) and non-CYP450 enzymes (flavin-containing monooxygenase [FMO] and aldehyde oxidase [AO]). Involvement of multiple enzymes can effectively decrease the risk of potential DDI in clinical trials. HMPL-689 was found to be neither a reversible nor a time-dependent inhibitor of major CYP450 isoforms except to be a weak reversible inhibitor on CYP2C8 (IC_{50} = 30.4 μM) and CYP2C9 (IC_{50} = 10.7 μM). HMPL-689 showed low potential to induce the activities of CYP isoforms of CYP1A2, CYP2B6, and CYP3A4 in human hepatocytes. Moreover, HMPL-689 showed low potential to interfere with efflux transport (efflux ratio <2.0) and no inhibition of breast-cancer resistance protein (BCRP), but also showed weak inhibition on P-glycoprotein (P-gp) (IC_{50} = 22.9 μM). Hence, the risk of drug interaction was predicted to be low. The preliminary results showed that 91% of HMPL-689 and its metabolites were recovered from urine, bile, and feces in rat at 96 hours following a single oral dose. In summary, HMPL-689 showed good absorption, low to medium clearance, extensive distribution, and no obvious accumulation in preclinical species. There was good agreement between the in vitro and in vivo studies. In in vitro human pharmacokinetic studies, HMPL-689 showed high permeability, low potential of efflux transport, good metabolic stability, medium PPB, and low potential of DDI. Based on the results from these studies, HMPL-689 was expected to possess good oral absorption, low clearance, high oral bioavailability, extensive tissue distribution, and low risk of DDI in humans.

2.2.3 Preclinical Toxicology

The safety profiles of HMPL-689 were evaluated in several *in vitro* and *in vivo* studies under GLP condition.

- HMPL-689 at 30 mg/kg caused transient and recoverable increase of systolic blood pressure in conscious beagle dogs in single oral administration in telemetered conscious beagle dog. HMPL-689 at the doses up to 10 mg/kg did not have any effect on cardiovascular system in conscious beagle dogs. Therefore, the no-observed-effect level (NOEL) of HMPL-689 on cardiovascular parameters in conscious beagle dog is considered to be 10 mg/kg.
- The hERG evaluation study results showed that HMPL-689 inhibited hERG currents with an IC_{50} of >30 μM.
- HMPL-689 up to 150 mg/kg did not exhibit any significant effects on CNS system compared with animals given the vehicle in a single oral dose study in Sprague-Dawley rats. The NOEL of HMPL-689 is considered to be 150 mg/kg in this rat study.

- HMPL-689 up to 120 mg/kg did not exhibit any significant effects on respiratory function in a single oral dose study in Sprague-Dawley rats compared with animals given the vehicle. The NOEL of HMPL-689 is considered to be 120 mg/kg in this study.
- The maximum tolerated dose (MTD) for HMPL-689 was 2000 mg/kg in rats, and 1000 mg/kg in dogs, respectively, in single dose toxicity studies.
- Sprague-Dawley rats were administrated daily of HMPL-689 at the dose of 3, 15, and 100 mg/kg/day for 4 weeks, followed by 4-week recovery period in a 4-week toxicity study. No mortality or moribund was found during the whole period of study. No abnormal change was found in clinical observation, body weight and food consumption. Changes in clinical pathology were mainly observed in females in the 100 mg/kg group, including increased white blood cell (WBC) count and percentages of monocytes, neutrophils, and that of reticulocytes, while there was a decrease in percentage of lymphocytes, hemoglobin, hematocrit, glucose, total protein, albumin, and albumin-globulin ratio. In bone marrow smear evaluation, increased eosinophil granulocyte cell counts were observed in females at 100 mg/kg. All above changes were reversible following a 4-week recovery period. The HMPL-689 related histopathological changes were observed as follows: changes of thymus, liver, and mandibular and mesenteric lymph nodes were observed in female at doses ≥3 mg/kg; in addition, histopathological change of testes was found in male at doses ≥15 mg/kg; histopathological changes in spleen could be found in female at doses ≥15 mg/kg and in male at 100 mg/kg, respectively. The histopathological changes in gastrointestinal system (stomach, duodenum, jejunum, ileum, cecum, and colon), Peyer's patches, bone marrow of sternum, tongue, and adrenal glands were only found in female at 100 mg/kg. After the 4-week recovery period, all those histopathological changes were recovered, except for the inflammatory cell infiltration in tongue, which persisted in female of 100 mg/kg with low incidence. Therefore, the no-observed-adverse-effect level (NOAEL) is considered to be 3 mg/kg with corresponding AUC_{0-t} of 1430 h•ng/mL for male rats. The low-observed-adverse-effect level (LOAEL) was considered to be 3 mg/kg with corresponding AUC_{0-t} of 6260 h•ng/mL for female rats. According to the exposure of NOAEL/LOAEL, the safety margins compared with the potential efficacy dose in the inhibition of the activation of B-cells in vivo were 3.0-fold (male) and 13.3-fold (female), respectively.
- Beagle dogs were administrated daily of HMPL-689 at the dose of 0.5, 3.5, and 25 mg/kg/day for 4 weeks, followed by 4-week recovery period in a 4-week toxicity study. The HMPL-689 related abnormal finding were observed as follows: decreased activity, decreased the percentage of basophiles and increased fibrinogen in animals treated at doses ≥3.5 mg/kg; and watery feces, color change (red) of feces, decreased body weight and food consumption, increased WBC count, percentage of neutrophil, aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH), companied with decreased percentage of lymphocyte, total protein, albumin, and albumin-globulin ratio in animals at dose 25 mg/kg. The above changes were reversible in surviving animals following a 4-week recovery period. The HMPL-689 related histopathological changes were observed in tongue, mandibular lymph nodes, spleen, liver, mesenteric lymph nodes, Peyer's patches, thymus, and testes at doses ≥3.5 mg/kg; in esophagus, intestines including duodenum, ileum, cecum, colon and rectum, lungs, bone marrow of sternum and femur at 25 mg/kg. After the 4-week recovery period, the HMPL-689 related changes still persisted in Peyer's patches at 3.5 mg/kg and in liver and

testes at doses ≥25 mg/kg. The NOAEL is considered to be 0.5 mg/kg with corresponding AUC_{0-t} of 550 (female) and 754 (male) h•ng/mL.

- HMPL-689 was not genotoxic in the in vitro bacterial reverse mutation study, an in vivo micronucleus evaluation in the 4-week repeated dose toxicity study in Sprague-Dawley rats up to 100 mg/kg, and a single-dose toxicity study in ICR mice (non-GLP) up to 2000 mg/kg. In a chromosome aberrant test, HMPL-689 could induce the increase the incidence of cells with aberrant chromosome at 240.0 μg/mL (the highest concentration tested) with high cell growth inhibition (>60%) at 4 hours with or without S9, but has no impact at all other concentrations. This concentration is far greater than the EC_{90} (ex vivo, HMPL-689 on B-cell activation in whole blood of naive female Wistar rats) of 16 ng/mL in rat (~15,000 fold).
- Sprague-Dawley rats were orally administered daily of HMPL-689 at doses of 3, 15, and 100 mg/kg/day in fertility and early embryonic developmental toxicity study. The no-observed-adverse-effect level (NOAEL) of HMPL-689 for general toxicity is considered to be 3 mg/kg/day in parental male and 15 mg/kg/day in female rat, respectively. The NOAEL of HMPL-689 for fertility and early embryonic development is considered to be 100 mg/kg/day.
- HMPL-689 was not phototoxic in an in vivo study with guinea pigs. In this study, HMPL-689 was administered as a single dose via oral gavage to guinea pigs at 5, 25, or 125 mg/kg. No skin reactions were observed at all time points in both non-irradiated and irradiated skin of all animals treated with the test article.

Overall, HMPL-689 was well tolerated in rat and dog following a single dose oral administration. Toxic findings were seen in repeat-dose animal safety evaluations in rats and dogs at higher doses and were found to be reversible. These findings can be readily monitored in the clinical studies and were fully or partially reversible upon drug withdrawal.

2.3 Clinical Experience of HMPL-689

See the investigator's brochure (IB) for up-to-date clinical experience for HMPL-689.

Study CCI [redacted] (Completed)

This was a phase 1, randomized, double-blind, placebo-controlled, first-in-human, single dose escalation study to investigate the safety, tolerability and PK of HMPL-689 in Australia (completed). The study enrolled 48 healthy volunteers who were randomized into HMPL-689 group or placebo group at a 3:1 ratio. Subjects received oral single doses of HMPL-689 or placebo in sequence at dose levels of 1, 2.5, 5.0, 10, 20, and 30 mg under fed condition.

Of 36 subjects in the HMPL-689 treatment group, 15 subjects (41.67%) experienced a total of 19 adverse events (AEs). Adverse events reported in at least one subject included upper respiratory tract infection (13.9%), headache (8.3%), dyspepsia (5.6%), oligospermia (5.6%), flatulence (2.8%), back pain (2.8%), musculoskeletal pain (2.8%), eczema (2.8%), skin burning sensation (2.8%), and eye irritation (2.8%). Adverse events that were assessed by the investigator as related to HMPL-689 were upper respiratory tract infection (8.3%), headache (5.6%), dyspepsia (5.6%), flatulence (2.8%), and back pain (2.8%). Alanine transaminase increase was noticed in 5.56% of subjects in the HMPL-689 group and 8.33% of subjects in the placebo group. Aspartate transaminase increase was noticed in 19.44% of subjects in the HMPL-689 group and 25% of

subjects in the placebo group; all of the ALT/AST increases were of Grade 1. No Grade ≥3 AE was reported. No dose limiting toxicity (DLT) was noted.

The single dose PK of HMPL-689 was evaluated in 36 healthy volunteers in the HMPL-689 treatment group under fed condition. HMPL-689 was absorbed after oral administration with a median T_{max} of 1.5 to 3 hours. The HMPL-689 exposures, as measured by C_{max} and AUC, increased with dose increase from 1 to 30 mg after single dosing. The geometric means of apparent volume of distribution (V_z/F) and apparent oral clearance (CL/F) were approximately 209-268 L and 18.2-23.0 L/h, respectively, across all dose levels. The geometric mean $t_{½}$ values were similar across dose levels, with values ranging from 7.06 to 9.37 hours.

Study CCI [redacted] (Completed)

This was a single-center, randomized, open-label, single-dose, 2-period crossover study conducted in China to evaluate the effects of food on the PK of HMPL-689. Healthy male subjects received a single oral dose of HMPL-689 30 mg (3 × 10 mg capsules) under fasting (at least 10 hours overnight fast) and fed conditions (total calories: 800 to 1000 calories with fat contributing to 50% of the total caloric content of the meal, consumed within 30 minutes prior to dosing). Each dose was separated by a washout period of 4 days.

Dosing HMPL-689 with food prolonged HMPL-689 t_{max} by 3.0 hours with median (range) of 1.0 (0.5 to 4.0) hour under fasted condition and 4.0 (1.5 to 8.0) hours under fed condition. Fed conditions decreased the C_{max} by 36% but did not alter HMPL-689 $AUC_{0\text{-inf}}$. These results suggest that HMPL-689 can be administered with or without food.

Study CCI [redacted] (Ongoing)

This is a phase 1, open-label study to assess the safety, PK, and preliminary efficacy of HMPL-689 administered orally in patients with relapsed or refractory lymphoma. This study includes 2 stages: a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). For Stage 1, a modified toxicity probability interval scheme-2 (mTPI-2) design is adopted for the dose escalation and MTD determination.

At the start of 2018-689-00US1, the study was ongoing at Stage 1 and 13 patients have received at least 1 dose of HMPL-689 and are evaluable for safety. The dose levels of HMPL-689 tested included 2.5 mg twice daily (BID), 5 mg BID and 5 mg once daily (QD). This data enabled the development of protocol 2018-689-00US1 (current protocol).

As of 30 Apr 2018, twelve patients (92.3%) treated with HMPL-689 experienced at least 1 treatment emergent adverse event (TEAE). Treatment emergent adverse events that occurred in more than 1 patient were blood bilirubin increased (38.5%), neutropenia (38.5%), asthenia (30.8%), leukopenia (30.8%), thrombocytopenia (30.8%), upper respiratory tract infection (30.8%), bilirubin conjugated increased (23.1%), cough (23.1%), proteinuria (23.1%), abdominal pain (15.4%), amylase increased (15.4%), anemia (15.4%), hypertension (15.4%), hypokalemia (15.4%), influenza syndrome (15.4%), pain (15.4%), and blood urine present (15.4%). Treatment emergent adverse events of Grade ≥3 reported by at least 1 patient included amylase increased (15.4%), hypertension (15.4%), AST increased (7.7%), back pain (7.7%), blood glucose increased (7.7%), left ventricular dysfunction (7.7%), leukopenia (7.7%), pain (7.7%), and thrombocytopenia (7.7%). Grade ≥3 TEAEs assessed as related to HMPL-689 by the investigators were amylase increased (15.4%), AST increased (7.7%), hypertension (7.7%), leukopenia (7.7%), thrombocytopenia (7.7%). Two DLTs (asymptomatic Grade 3 amylase increased) were observed

in 6 patients at the dose level of 5 mg BID, and no DLT was observed at the dose levels of 2.5 mg BID or 5 mg QD.

Seven of the 13 patients were efficacy evaluable. The best overall responses were observed in 7 patients, including 6 with partial response (PR)/partial response with lymphocytosis (PR-L) and 1 with stable disease (SD). PR/PR-L occurred at 2.5 mg BID (1 SLL and 1 MCL), 5 mg BID (2 MCL), and 5 mg QD (1 MCL and 1 CLL).

As of 30 Apr. 2018, the preliminary PK data for 2.5 mg BID, 5 mg BID, and 5 mg QD on Day 1 and Day 15 were available but have not been validated and are subject to change. Compared to the single dose PK data obtained from Australian healthy volunteers in Study CCI [redacted], the PK profile on Day 1 in Chinese patients with lymphoma was similar to that in male healthy volunteers in Australia with regard to t½ and exposures (C_{max} and AUC) at the equivalent dose level. After multiple oral doses for 15 days, the accumulation ratio was around 1-2.

As of March 2021, this ongoing Phase I trial of HMPL-689 in China (CCI [redacted]) has completed dose escalation with a RP2D of 30mg QD. As of this cutoff, 79 patients with relapsed or refractory NHL (FL, marginal zone lymphoma [MZL], MCL, DLBCL) have so far received the RP2D dose level in the dose escalation or expansion phase of this trial. Of these 60 patients had completed at least one tumor assessment. The objective response rate (ORR) rate for this group was 51.7% (31/60) and CR rate 13.0% (8/60). In 18 patients with FL, the ORR was 77.8% (14/18) and CR rate 38.9% (7/18). In MZL, 6 out of 12 patients have responded (ORR 50.0%). In mantle cell lymphoma, 4 out of 5 patients have responded (ORR 80.0%). The most common AEs (incidence ≥ 10%) in subjects treated with the RP2D (n=79) included neutropenia (28.8%), leukopenia (22.7%), upper respiratory tract infection (12.1%) and hypertriglyceridemia (10.6%). TEAEs of Grade ≥3 (≥ 5%) were neutropenia (13.6%) and rash (6.1%). The other Grade ≥3 TEAEs of interest (<5%) reported of were pneumonia 4.5% and diarrhea 1.5%. There were no reported Grade ≥3 TEAEs of interest of ALT/AST elevation, hypertension, colitis or pneumonitis.

2.4 Study Rationale and Benefit-Risk Assessment

Class I phosphatidylinositol 3-kinase (PI3K) is a lipid kinase with a catalytic subunit that exists in 4 different isoforms: α, β, δ, and γ. Activation of PI3K generates lipid second messengers at the cell membrane that recruit and activate multiple intracellular enzymes that are regulators of cell proliferation, survival, and motility. The α and β isoforms are widely expressed in many tissues, and the phosphatidylinositol 3-kinase γ isoform (PI3Kγ) has a particular role in T-cell activation, PI3Kδ expression is largely restricted to hematopoietic cells (Brown 2014). In B-lymphocytes, the δ isoform (PI3Kδ) plays a central role in normal B-cell development and function, transducing signals from the B-cell receptor as well as from receptors for various cytokines, chemokines, and integrins (Durand 2009, Bilancio 2006). PI3Kδ signaling pathways are commonly hyperactive in B-cell malignancies, making inhibition of PI3Kδ a promising target in the therapy of B-cell NHL (Lannutti 2011, Hoellenriegel 2011).

PI3Kδ inhibitors have proven activity in relapsed/refractory lymphoma setting, with four agents receiving accelerated approval from the United States Food and Drug Administration (FDA) for the treatment of follicular lymphoma, (idelalisib, copanlisib, duvelisib and umbralisib). Additionally, umbralisib is also approved in the United States for the treatment of MZL.

In the idelalisib phase 2 study in patients with relapsed iNHL, 125 patients, including 72 FL, 28 SLL, 15 MZL, and 10 lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia

(LPL/WM), were enrolled and treated with idelalisib as a single agent (Gopal 2014). The ORR was 57% (71/125 patients), with 6% meeting the criteria for a CR. The median time to a response (TTR) was 1.9 months, the median DoR was 12.5 months, and the median progression-free survival (PFS) was 11 months. Similar response rates were observed across all subtypes. The most common adverse events of grade 3 or higher were neutropenia (27%), elevations in transaminase levels (13%), diarrhea (13%), and pneumonia (7%). For the patients with relapsed/refractory MCL enrolled in phase 1 study, idelalisib also showed tolerable toxicity and anti-tumor activities: patients without DLT and no evidence of disease progression after 48 weeks enrolled in the extension study (Kahl 2014). Common Grade ≥3 AEs included diarrhea (45%), decreased appetite (75%), transaminase levels elevations (33%). ORR was 40% (16/40 patients), with CR 5% (2/40). Median DoR was 2.7 months, median PFS was 3.7 months, and 1-year PFS was 22%. Based on this study, FDA approved idelalisib for the treatment of patients with relapsed FL or SLL who have received at least two prior systemic therapies.

In the phase 3 study among patients with relapsed CLL who were less able to undergo chemo-therapy, the combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival (mean PFS: not reached in the idelalisib group and 5.5 months in the placebo group [hazard ratio for progression or death in the idelalisib group = 0.15; P <0.001]), ORR (81% vs. 13%; odds ratio, 29.92; P <0.001), and overall survival (OS) at 12 months (92% vs. 80%; hazard ratio for death, 0.28; P = 0.02). Serious adverse events occurred in 40% of the patients receiving idelalisib and rituximab and in 35% of those receiving placebo and rituximab. Based on the study results, FDA approved idelalisib for the treatment of patients with relapsed CLL, in combination with rituximab (Furman 2014).

In a single-arm, multicenter, phase 2 clinical trial to evaluate the efficacy of copanlisib (PI3K α/δ inhibitor) in relapse NHL, a total of 142 patients were enrolled, including 104 FL patients, who have received at least two prior treatments, including rituximab and an alkylating agent (Dreyling 2017). The ORR in FL patients was 59%, with 14% CR and 44% PR. The median DoR was 12.2 months (range 0+ to 22.6 months). The median TTR was 1.7 months (range 1.3 to 9.7 months). Safety data were collected in 168 adults with FL and other hematologic malignancies treated with copanlisib. Serious adverse reactions were reported in 44 (26%) patients. The most frequent serious adverse reactions that occurred were pneumonia (8%), pneumonitis (5%), and hyperglycemia (5%). The most common adverse reactions (≥20%) were hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia. Based on this study, FDA approved copanlisib for the treatment of patients with relapsed FL who have received at least two prior systemic therapies.

In a phase 2, multi-center, open-label trial to evaluate the activity and safety of duvelisib (PI3K α/γ inhibitor) in patients with relapsed/refractory iNHL a total of 129 patients were enrolled, including FL, MZL, and SLL. All enrolled patients were double refractory to rituximab and to either chemotherapy or radioimmunotherapy. The ORR across all indications was 47.3% (42.2% FL, 38.9% MZL). The estimated mDOR was 10 months with an estimated mPFS of 9.5 months. Safety data revealed diarrhea (48.8%), nausea (29.5%), neutropenia (28.7%), fatigue (27.9%), and cough (27.1%) as the most common TEAEs. At least one ≥ grade 3 TEAE was experienced in 88.4% of patients, with the most common being neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%) (Flinn 2019).

In a phase 2, multi-center, open-label trial to evaluate the safety and efficacy of umbralisib in previously treated NHL patients, a total of 208 patients were enrolled, including 69 MZL, 117 FL, and 22 SLL. MZL patients were refractory to at least one line of anti-CD20, and FL/SLL patients were refractory to at least two lines of therapy, including an anti-CD20. The ORR in FL patients was 45.3% with 5.1% CR and DoR of 11.1 months (range 8.3-15.6 months). The median TTR was 2.8 months (range 2.7 to 2.9). The ORR in MZL patients was 49.3% with 15.9% CR and DoR not yet reached at time of publication. The median TTR was 2.8 months (range 2.7 – 2.9). Safety data revealed serious adverse events in 28.1% of patients, with 24.6% ≥ grade 3. The most common ≥ grade 3 AEs were neutropenia (11.5%), diarrhea (10.1%) and increased ALT/AST (7.2%). Other AEs of interest included pneumonitis (all grade 1.4%; ≥ grade 3 1.0%), and colitis (all grade 1.4%; ≥ grade 3 0.5%) (Zinzani 2020).

Overall, approved PI3k-δ inhibitors have demonstrated a modest ORR in the range of 40% to 50% in FL and MZL. However, they demonstrate a low CR rate of 1-16% and mPFS of less than 12 months. While these agents represent a manageable toxicity profile, high rates of diarrhea, colitis, and hepatic toxicity results in a high rate dose reduction and treatment discontinuation, thereby impacting the long term benefit. Therefore, there is room for a more efficacious and tolerable PI3K-δ inhibitor for treatment of NHL (Dreyling 2017, Zinzani 2020, Flinn 2019).

HMPL-689 is a PI3Kδ inhibitor with different molecular structure as compared with idelalisib or duvelisib. Preclinical data shows that HMPL-689 is a small molecule inhibitor with high potency, favorable pharmacokinetic and drug safety profile. The ratio of HMPL-689 biochemical activity in PI3Kδ was >100 times stronger than the other PI3K isoforms. Broad kinase selectivity studies demonstrated HMPL-689's high PI3Kδ selectivity that is better than idelalisib and duvelisib. Improved isoform selectivity can minimize serious infection that is seen with duvelisib as a result of inhibiting PI3Kγ and causing immune suppression. In the ongoing Phase I study (CCI [redacted]) out of 18 FL patients ORR of 77.8% (14/18) and CR rate 38.9% (7/18) was achieved as of March 2021. In MZL, 6 out of 12 patients responded (ORR 50.0%). In mantle cell lymphoma, 4 out of 5 patients responded (ORR 80.0%). The evolving clinical data for HMPL-689 from Study CCI [redacted] suggests encouraging activity in NHL sub-types such as FL, MZL, MCL and CLL/SLL, with a very tolerable safety profile. High PIK3-*δ* expression has also been noted consistently in some sub-types of T-cell lymphoma such as peripheral T-cell lymphoma (PTCL) (Huang 2020). Current approved therapies for relapsed/refractory PTCL do not provide consistent efficacy benefit across all sub-types, resulting in a poor overall 5-year survival rate of 10-30% (Coiffier 2014). In phase 1/2 studies, PIK3-inhibitors have demonstrated promising clinical activity with overall responses of ~30% to 50% and an acceptable safety profile (Horwitz 2018, Dreyling 2017), suggesting a role for PIK3-inhibitors such as HMPL-689 in this setting.

Similarly, the paucity of treatment options for relapsed/refractory cutaneous B-cell lymphoma (CBCL) and the potential for PI3K inhibitors to benefit these patients supports the evaluation of HMPL-689 in the study 2018-689-00US1 (Dummer 2012).

Overall, given the importance of the PI3Kδ pathway in the lymphomas, HMPL-689's significant efficacy in the preclinical cell lines and preliminary efficacy in lymphoma patients, coupled with its desirable pharmacokinetic and safety profile, HMPL-689 warrants further investigation in clinical studies to fully characterize its potential as a novel small-molecule oral therapy for lymphomas.

3 OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints

Tier	Objectives	Endpoints
Primary – Dose Escalation	To determine MTD and/or RP2D of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma	• Incidence of DLTs • Safety (including but not limited to TEAEs, treatment-related adverse events [TRAEs], SAEs, treatment-related SAEs [TRSAEs], and lab abnormalities)
Primary – Dose Expansion	To further evaluate safety and tolerability of HMPL-689 at MTD in patients with relapsed, refractory, or resistant lymphoma	• Safety, including TEAEs and TRAEs
Secondary	To assess preliminary efficacy of HMPL689 in patients with relapsed, refractory, or resistant lymphoma overall and by lymphoma sub-types as assessed by investigator	• ORR • TTR • DoR • CBR • PFS
	To characterize PK parameters of HMPL-689 in patients with relapsed, refractory, or resistant lymphoma at both dose escalation and dose expansion stages	• Concentration-time profiles and PK parameters after single dose and at steady state
	To evaluate the effect of HMPL-689 on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QTc intervals	• QTc interval and HMPL-689 concentration

Abbreviations: CBR = clinical benefit rate; DLT = dose-limiting toxicity; DoR = duration of response; MTD = maximum tolerated dose; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetic; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; TRSAE = treatment-related serious adverse event; TTR = time to response.

4 STUDY DESIGN

4.1 Overall Study Design

This is a phase 1, open-label, multicenter study of HMPL-689 administered orally daily to patients with relapsed, refractory or resistant lymphoma.

This study will consist of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). Both Stage 1 and Stage 2 include the following periods: screening period, treatment period, safety follow-up period, and extended PFS follow-up period, if applicable, as defined in Appendix 1.

The study duration is estimated to be approximately 48 months.

4.1.1 Dose Escalation Stage (Stage 1)

Dose escalation will be performed according to an mTPI-2 (Yang 2015). HMPL-689 dose escalation will be titrated using a modified Fibonacci design allowing dose increments in subsequent dose levels as listed in Table 2. The guidelines used for dose escalation are shown in Figure 1.

Table 2 Proposed Dose Escalation Scheme

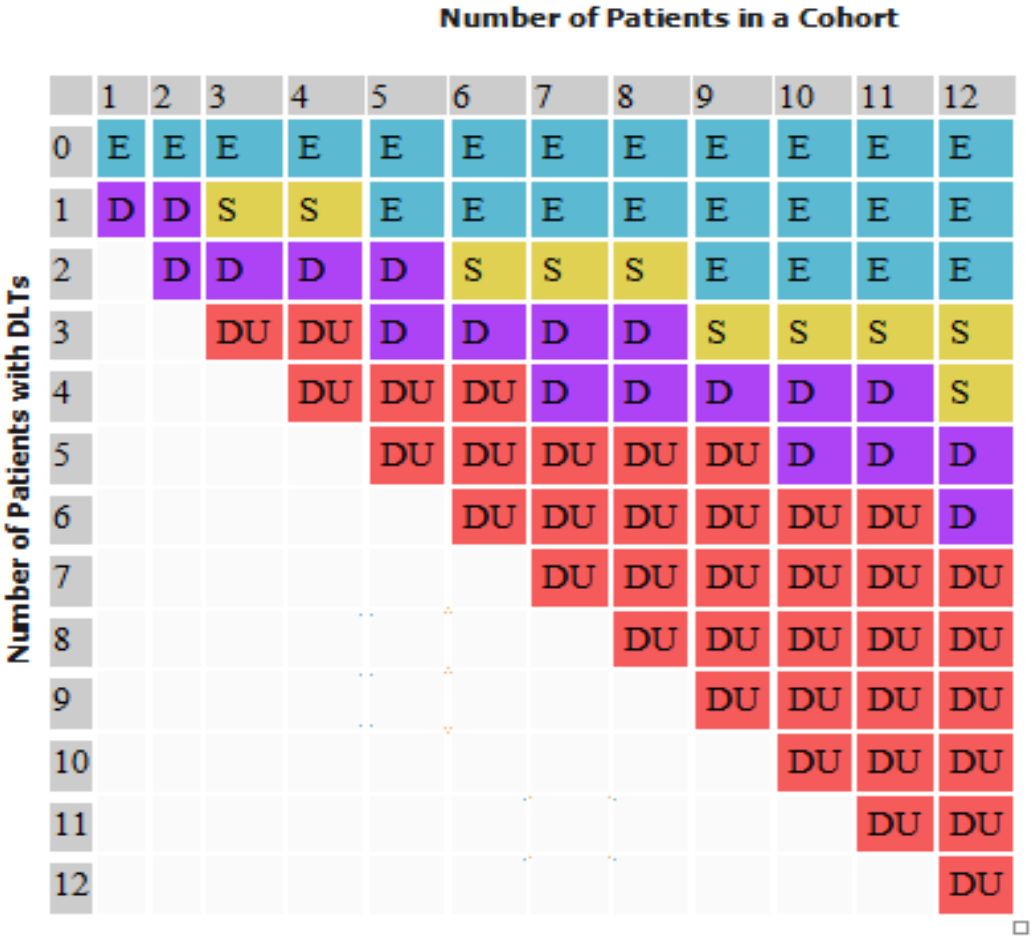
Cohort	Dose Level[a]	Route of Administration
-1	2.5 mg QD	Orally, with water
1	5 mg QD	Orally, with water
2	10 mg QD	Orally, with water
3	15 mg QD	Orally, with water
4	20 mg QD	Orally, with water
5	25 mg QD	Orally, with water
6	30 mg QD	Orally, with water
7	35 mg QD	Orally, with water
8	40 mg QD	Orally, with water
9	45 mg QD	Orally, with water
10	50 mg QD	Orally, with water
X[b]	XX[b]	Orally, with water

Abbreviations: PK = pharmacokinetic; QD = once daily; SRC = safety review committee.

[a] The actual next dose will be discussed and decided by the investigators and sponsors based on all previous available data.

[b] The need for dose escalation beyond 50 mg QD, or other regimens, such as twice daily, will be evaluated and determined by the SRC based on all available cumulative clinical safety, PK, and efficacy data.

Figure 1 mTPI-2 Decision Chart for Selection of Dose



DLT = dose limiting toxicity, E = escalate to the next higher dose; S: Stay at the same dose, D = de-escalate to the previous lower dose, DU = de-escalate to the previous lower dose and the current dose will never be used again in the trial.
Target toxicity probability = 30%; epsilon 1 = 0.05; epsilon 2 = 0.05.

The design characteristics of mTPI-2 are as follows:

- The maximum sample size for this stage will be determined by the sponsor and investigators, based on the accumulated data and the mTPI-2 method (Ji 2013). The maximum recommended sample size under mTPI-2 design is k × (d + 1), where k denotes the cohort size and d denotes the number of doses. In this study, the minimum cohort size is 3.
- The equivalence interval of toxicity probability for MTD is (25%, 35%). This interval is derived based on the following parameters:
  - The target probability of toxicity (p_T) is set to 30%.
  - Both epsilon 1 (ε1) and epsilon 2 (ε2) are set to 0.05.
- This stage will end when any of the following criteria is met:
  - The dose level 1 demonstrates an excessive toxicity, i.e., 3 DLTs are observed out of the first 3 patients at dose level 1.

- The maximum sample size is reached.
- The MTD and/or RP2D are confirmed.

The rules applied in the dose escalation stage are as follows:

- The starting dose is dose level 1: 5 mg QD.
- If a lower dose is needed upon results from dose level 1, dose level -1 will be explored.
- Three patients will be enrolled for the initial cohort (dose level 1).
- At the end of the DLT assessment window for a dose level, the decision on the dose of the next dose level will follow the rule specified in Figure 1, which leads to enrollment of another 3 patients at the next step.
- In the event that the first two patients within a given dose level experience DLT events but the third patient has not yet begun protocol treatment, the third patient should receive a lower dose per the mTPI-2 algorithm.

At the end of Stage 1, the MTD will be determined based on the number of patients treated and the number of experienced DLTs at each dose level.

Stopping rules for individual patients in the dose escalation stage are located in Section 5.8.3.1. Stopping rules for dose cohorts or for the study in the dose escalation stage are available in Section 5.8.4.1.

4.1.1.1 Intra-patient Dose Escalation

Intra-patient dose escalation to a higher dose level may be permitted by the sponsor, provided that the current dose level the patient is on has been cleared of DLT (safe and tolerable), and the higher dose level cohort being considered has also been cleared of DLT (safe and tolerable) prior to the start of that intra-patient dose escalation. There must be at least 28 days in-between the last dose of the current/lower dose level and the start of next/higher dose level and the patient must have tolerated the current/lower dose level.

4.1.1.2 Definition of Dose Limiting Toxicity

Dose limiting toxicities are defined as the occurrence in the DLT assessment window of any of the following TEAEs, unless equivocally due to underlying malignancy or an extraneous cause:

a. Non-hematologic toxicity: All non-hematologic TEAEs of Grade 3 or greater with the exception of:
   i. Grade 3 nausea or vomiting that can be controlled by supportive therapy
b. Hematologic toxicity:
   i. Grade 4 neutropenia lasting for more than 5 days
   ii. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding event or requiring platelet transfusion
   iii. Grade ≥3 febrile neutropenia (defined as ANC <1000/mm^3 with a single temperature > 38.3ºC [101°F] or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour)
   iv. Grade 4 anemia not explained by underlying disease
c. Any TEAE requiring a dose delay of ≥15 days
d. Any case of Hy's Law

4.1.1.3 Dose Limiting Toxicity Assessment Window

For all patients in Stage 1, DLTs will be assessed during a DLT assessment window of 28 days (i.e., from Cycle 1, Day 1 [the day of first administration of treatment] through Cycle 1, Day 28).

4.1.1.4 Definition of a DLT-Evaluable Patient

For decisions on dose escalation, each dose cohort shall present protocol-required number of DLT-evaluable patients. Any patient is DLT evaluable if he/she meets the following criteria:

A patient is DLT evaluable if he/she:

- has received at least 75% of the assigned dose of study treatment during the DLT assessment window (i.e., Days 1-28);

  or

- has not completed the DLT assessment period due to a DLT.

Patients who are not DLT evaluable in a dose cohort will be replaced to guarantee the protocol-required number of DLT-evaluable patients for each dose cohort.

4.1.1.5 Dosing Beyond Cycle 1

Patients who complete DLT assessment window and are deemed by the investigator to be benefiting from HMPL-689 treatment may continue with HMPL-689 treatment until disease progression, death, intolerable toxicity, at investigator's discretion that the patient can no longer benefit from the study treatment, withdrawal of consent, or the end of study, whichever occurs first. Conversely, if, in the opinion of the attending principal investigator, the patient may receive clinical benefit from a higher dose, then, at the request of the principal investigator and with the approval of the sponsor, the patient may be able to participate in intra-patient dose escalation (Section 4.1.1.1).

During the study treatment period, including the DLT assessment window, patients will not be allowed to make up missed doses.

4.1.1.6 Definition of Maximum Tolerated Dose

The recommended MTD is the dose with a posterior toxicity probability closest to the target toxicity probability $\boldsymbol{p_T}$, i.e., closest to 30%. In case all doses have toxicity probabilities greater than ($\boldsymbol{p_T}$ + ε2), i.e., 35%, no dose will be considered as MTD.

Posterior toxicity probability at each dose level will be estimated based on a beta posterior distribution and application of pooled adjacent violator's algorithm (Yang 2015).

4.1.1.7 Definition of Recommended Phase 2 Dose

The decision regarding the RP2D will take the following into consideration:

- MTD, if reached;
- Pharmacokinetics with or without associated safety and preliminary efficacy findings.

These criteria constitute the basis for RP2D determination. Both the sponsor and the safety review committee (SRC) (Section 4.1.3) must agree on the RP2D.

4.1.2 Dose Expansion Stage (Stage 2)

The safety, tolerability, PK, and preliminary efficacy of HMPL-689 at the MTD/RP2D will be further evaluated in patients with relapsed, refractory, or resistant NHL.

In the dose expansion stage, approximately CCI patients will be enrolled in the following cohorts (Table 3), with approximately the indicated number of patients enrolled per cohort.

CCI

Table 3 Number of Planned Patients Enrolled Per Cohort

CCI

[a] Patients with prior BTK inhibitor exposure should be either refractory or intolerant to BTK inhibitor therapies listed in Appendix 16.

[b] Relapsed, refractory, or intolerant to a BTK inhibitor, where intolerance is defined as treatment discontinuation for ≥ 14 days without disease progression due to ≥ 1 Grade 3 or ≥ 2 Grade 2 non-hematologic toxicities, ≥ 1 Grade 3 neutropenia with infection or fever, or ≥ 1 Grade 4 hematologic toxicity.

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

Patients will receive oral doses of HMPL-689 QD at the RP2D for continuous 28-day treatment cycles until disease progression, death, intolerable toxicity, at investigator's discretion that the patient can no longer benefit from the study treatment, patient withdrawal from the study, or the end of study, whichever occurs first.

Stopping rules for individual patients in the dose expansion stage are located in Section 5.8.3.2. Stopping rules for dose cohorts or for the study in the dose expansion stage are available in Section 5.8.4.2.

4.1.3 Safety Monitoring

Safety monitoring and dose escalation determination will be conducted by a SRC, which consists of the sponsor's medical monitor, drug safety lead, PK scientists, and the sites' Principal Investigators (PIs) or delegate, as applicable. Safety will be monitored continuously throughout the conduct of this study by the SRC. There will be periodic reviews of emerging data on safety, PK, drug exposure, target engagement, pharmacodynamics, and clinical response to determine continuation (or otherwise) of an individual participant, cohort arm, or entire expansion stage.

The SRC for dose escalation stage may extend to the expansion stage or a new one may replace this SRC, with the same mandate.

4.1.4 Lifestyle Management

Full assessment of extensive non-clinical studies indicated HMPL-689 has no phototoxic effects. Furthermore, experience from ongoing clinical studies in China and Australia also confirm that this study drug lacks any phototoxic effect. Nonetheless, patients enrolled in this study are advised to avoid unnecessary long-term and direct exposure to sunlight or any other source of ultraviolet (UV) light during their participation in the study and until 30 days after the last dose of study drug. Patients are also encouraged to wear sunglasses and apply sunscreen products with protective coefficient of at least SPF 15 whenever possible.

4.1.5 Tumor Assessment and Response Evaluation

Tumor assessment and response evaluation will be performed using the International Workshop on CLL guideline for patients with CLL (Hallek 2008, Cheson 2012), the consensus of International Workshops on WM (IWWM-7 consensus) (Dimopoulos 2014), for patients with LPL/WM, and the Lugano response criteria for patients with other lymphomas (Cheson 2014). Tumor assessment will be conducted every 8 weeks (±7 days) for the first 24 weeks and every 12 weeks (±7 days) thereafter. -

Determination of disease progression will occur locally by the investigator in accordance with respective disease criteria.

4.1.6 Safety Follow-Up Period

The safety of all enrolled patients will be closely monitored after the inform consent has been obtained until 30 days post last treatment dose or the initiation of new antineoplastic therapy, whichever comes earlier. After the safety follow-up period, investigators shall only report the follow-up of unresolved SAEs that are related to prior study treatment of HMPL-689. All AEs will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

4.1.7 Extended Progression-Free Survival Follow-Up Period

Patients who discontinue HMPL-689 treatment due to reasons other than disease progression will enter the extended PFS follow-up period. During this period, tumor assessment will be conducted quarterly until disease progression, death, the end of the study or the initiation of new anti-neoplastic therapy, whichever is earlier.

Upon implementation of Protocol Amendment 5, this assessment will no longer be required.

4.2 Rationale for the Starting Dose and Dosing Schedule

The starting dose of this multiple doses study in human is determined according to the final result of the single dose study in healthy volunteers, the preliminary result of the multiple doses study in patients with lymphoma, as well as the result of the non-clinical toxicity studies.

In the HMPL-689 single dose escalation first-in-human study (CCI [redacted]), single dose of HMPL-689 30 mg was well tolerated with no DLT or SAE noted. The exposures of HMPL-689 measured by geometric mean $AUC_{0\text{-}24h}$ values in human at dose levels of 1, 2.5, 5, 10, 20 and 30 mg were 39.9, 98.2, 195, 446, 877, and 1280 h•ng/mL, respectively. The geometric mean $t_{½}$ of HMPL-689 was around 7-9 hours.

In the multiple dose escalation study (CCI [redacted]), 2 DLTs were observed at 5 mg BID, and no DLT was observed at 2.5 mg BID or 5 mg QD. Re-challenging of 5 mg BID and evaluating of 10 mg QD were ongoing at the data cut-off date of 30 April 2018. The PK profile in Chinese patients with lymphoma on Day 1 was similar to that in male healthy volunteers in Australia with regard to $t_{½}$ and exposures (C_{max} and AUC) at the equivalent dose levels. After multiple oral doses for 15 days, the accumulation ratio was around 1-2. Partial responses were observed in all dose levels tested, including 2.5 mg BID, 5 mg BID and 5 mg QD.

In HMPL-689 4-week toxicity studies, the NOAEL were 0.5 mg/kg/day in dogs and 3 mg/kg/day in male rats, respectively. The $AUC_{0\text{-}24h}$ was 754 h•ng/mL in male and 550 h•ng/mL in female for dogs, 1430 h•ng/mL in male rats for corresponded NOAELs, respectively.

According to total exposure of HMPL-689 in human and in preclinical toxicity studies, and the different protein binding rates of HMPL-689 in rat, dog and human, which was around 89.1%, 88.5% and 93.1%, respectively, the human equivalent dose of NOAEL, estimated by free exposure of HMPL-689, is likely to be 20-50 mg/day.

Based on the data above, HMPL-689 5 mg QD was selected as the initial dose in this study. A treatment cycle is defined as 28 days of continuous dosing.

4.3 Rationale for Selection of Patient Population

The clinical data have indicated that PI3K is abnormally activated in B-cell lymphomas. *In vitro* experiments have also demonstrated that PI3K molecule plays major role in activation and proliferation of B-NHLs, as previously discussed (Section 2.3). For example, down-regulation of PI3K was able to reduce proliferating signal as well as the expansion of DLBCL cells and spontaneous lymphoma cells from transgenic mice. These experiments indicate that hyperactivated PI3K or PTEN deletion plays important role in promoting activation of B-NHLs. Therefore, inhibition of PI3K activation in B-NHLs may block signal transduction, resulting in inhibition of B lymphoma cell proliferation or lead to induction of apoptosis in tumor cell. This approach may provide a powerful tool for treatment of B-cell lymphomas.

The patient population of Stage 1 (i.e., patients with relapsed, refractory or resistant lymphoma) has been selected because these patients have exhausted all approved therapeutic options available, and offered by standard of care. Based on previous clinical data of HMPL-689 in a similar population, HMPL-689 might be offered to these patients as an alternative therapeutic options. The inclusion criterion of Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 has been selected to facilitate attribution of toxicities to disease or the introduction of this agent.

Patients with relapsed, refractory or resistant CLL/SLL, MCL, FL, MZL, PTCL, CBCL, and WM/LPL were selected for Stage 2 based on the preclinical and clinical data (Sections 2.2 and 2.3), which suggest that patients with these types of NHL are more likely to benefit from the treatment of PI3Kδ inhibitor.

4.4 End of Study

The end of the study is defined as 18 months after the last patient has been enrolled in the study or all patients have discontinued the study treatment, whichever comes earlier.

5 MATERIALS AND METHODS

5.1 Patients

CCI

[redacted]

5.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

1. Signed Informed Consent Form (ICF);
2. Age ≥18 years;
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
4. Histologically confirmed NHL of the following sub-types CLL/SLL, FL (grade 1-3a), MCL, MZL, LPL/WM, PTCL or CBCL;
   - Patients with CLL/SLL, FL (grade 1-3a), MCL and LPL/WM must have received at least 2 prior lines of systemic therapy.
   - Patients with MZL must have received at least 1 prior line of systemic therapy that includes an anti-CD20 monoclonal antibody agent.
   - Patients with PTCL and CBCL must have received at least 1 prior line of systemic therapy.
5. Patients with relapsed, refractory, or resistant NHL, as defined below:
   - Refractory to any prior regimen, defined as no response (complete response [CR] or partial response [PR]) to previous therapies, or progression within 6 months of completion of the last dose of prior therapy.
   - Those who can no longer tolerate/withstand cytotoxic chemotherapy and or available standard of treatment/care (SoT/SoC), where safety profile and risks of toxicity of other treatment options far outweigh any possible clinical benefit.
   - Those with no curative SoT or no reasonable access to available treatments, in particular, those who will benefit from this class of compound, in the opinion of the attending investigator.
6. In the dose expansion stage, patients must have measurable disease for objective response assessment, except for patients with CLL and WM/LPL

   NOTE: measurable disease with FL, MCL, MZL, PTCL, CBCL or SLL defined as at least 1 bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by computerized tomography [CT] scan), as defined in Appendix 7
7. Expected survival of more than 24 weeks as determined by principal investigator

8. Patients with prior treatment with any PI3Kδ inhibitors are eligible for dose escalation. However, during dose expansion, only patients that discontinued PI3Kδ inhibitor for reasons other than disease progression are eligible.
9. Male patients must use a condom and female patients of childbearing potential must agree to use highly effective contraceptive measures that result in a low failure rate (<1% per year) when used consistently and correctly, from the screening period, through the entire study period, and for 30 days after the last dose of study drug. These highly effective contraceptive measures, as defined by the Clinical Trials Facilitation Group (CTFG)*, include combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD) or intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, a vasectomized partner, or sexual abstinence if in the preferred and usual lifestyle of the patient. These same criteria are applicable to partners of patients involved in this clinical study if that partner is of childbearing potential. Postmenopausal females (no menses for 12 months without an alternative medical cause) and surgically sterilized females are exempt from this criterion.
   *Note: In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

5.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients with primary central nervous system (CNS) lymphoma;
2. Any of the following laboratory abnormalities:

   - Absolute neutrophil count $<1.0 \times 10^9$/L
   - Hemoglobin < 80 g/L
   - Platelets $<50 \times 10^9$/L

   NOTE: In the dose expansion stage, patients with cell counts below the thresholds listed above may be considered eligible if, in the investigator's opinion, the reason is bone marrow infiltration. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval by the sponsor will a patient with cell counts below the thresholds be enrolled in the study.

   NOTE: In the dose expansion stage, patients with ≤Grade 2 neutropenia per CTCAE version 5.0 and/or thrombocytopenia and with confirmed bone marrow infiltration are eligible.

3. Inadequate organ function, defined by the following:

   - Total bilirubin >1.5 times the upper limit of normal (× ULN), with the following exception:
     - Patients with known Gilbert's disease who have serum total and direct bilirubin level ≤ 2.5 × ULN and normal AST and ALT can be enrolled.

- AST or ALT > 2.5 × ULN, with the following exception:
  - In the dose expansion stage, patients with documented disease infiltration of the liver may have AST and ALT levels ≤5 × ULN.
- Estimated creatinine clearance (CrCl) per Cockcroft-Gault
  - Dose escalation stage of trial (Stage 1) – CrCl <40 mL/min
  - Dose expansion stage of trial (Stage 2) – CrCl <30 mL/min

4. International normalized ratio (INR) >1.5 × ULN, activated partial thromboplastin time (aPTT) >1.5 × ULN;

   - Patients requiring anticoagulation therapy but with a stable INR within the recommended range according to the local guideline are eligible.

   NOTE: Patients may be considered for this study if kidney function is impaired but this impairment is believed to be a result of the patient's underlying disease. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval by the sponsor will a patient with impaired kidney function due to underlying disease be enrolled in the study.

5. Serum amylase or lipase >ULN at screening or known medical history of serum amylase or lipase >ULN;

   NOTE: Patients with known medical history of serum amylase or lipase >ULN are eligible in the dose expansion stage.

6. Patients with presence of second primary malignant tumors within the last 2 years, with the exception of:

   - Basal cell carcinoma of the skin
   - Squamous cell carcinoma of the skin
   - Carcinoma in situ of the cervix
   - Carcinoma in situ of the breast

7. Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or cytomegalovirus (CMV); Active infection is defined as one requiring treatment with antiviral therapy, presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody), or CMV or HCV antibody

   - Patients who are positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV deoxyribonucleic acid (DNA). These patients will require HBV DNA PCR monitoring, as per local standards
   - Patients who are positive for CMV or HCV serology are eligible only if testing for CMV DNA or HCV RNA is negative.

8. Any anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, vaccine, or radiotherapy within 3 weeks prior to initiation of study treatment;
9. Any granulocyte colony-stimulating factor treatment/blood transfusion within 7 days before the screening hematology test;

10. Any steroid therapy or approved targeted small molecule agents for anti-neoplastic intent within 7 days or approximately 5 half-lives, whichever is longer, prior to initiation of study treatment;
11. Prior use of any drug that is a strong inducer of CYP3A4 or strong inhibitor of CYP3A4 within 2 weeks prior to initiation of study treatment (3 weeks for St John's Wort) (refer to Appendix 8);
12. Prior autologous transplant within 6 months prior to initiation of study treatment;
13. Prior allogeneic stem cell transplant within 6 months prior to initiation of study treatment or with any evidence of active graft versus host disease or requirement for immunosuppressants within 21 days prior to initiation of study treatment;
14. Clinically significant active infection (e.g., pneumonia) or interstitial lung diseases (including drug induced pneumonitis);
15. Major surgical procedure within 4 weeks prior to initiation of study treatment;
16. Treatment within a clinical study of an investigational agent or using an investigational device within 30 days prior to initiation of the current study treatment;
17. Adverse events from prior anti-neoplastic therapy that have not resolved to Grade ≤ 1, except for alopecia;
18. Pregnant (positive urine or serum beta human chorionic gonadotropin [β-HCG] test) or lactating women;
19. New York Heart Association (NYHA) Class II or greater congestive heart failure;
20. Congenital long QT syndrome or corrected QT interval (QTc) >470 msec;
21. Currently use medication known to cause QT prolongation or torsades de pointes (see full list at http:// www.crediblemeds.org);
22. History of myocardial infarction or unstable angina within 6 months prior to initiation of study treatment;
23. History of stroke or transient ischemic attack within 6 months prior to initiation of study treatment;
24. Inability to take oral medication, prior surgical procedures affecting absorption, or active peptic ulcer disease;
25. History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis);
26. Patients with ongoing chronic gastrointestinal diseases;
27. Legally protected adults;
28. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk of treatment complications.

5.2 Study Treatment

5.2.1 Formulation, Packaging, and Handling

HMPL-689 capsules of 2 strengths (2.5 mg and 10 mg) will be used in this clinical study. The capsules are packaged in white high-density polyethylene (HDPE) bottles. The capsules are composed of widely used pharmaceutical excipients (United States pharmacopeia [USP] grade or equivalent) and HMPL-689 drug substance. The drug will be stored at temperatures between 10°C and 30°C and should remain in its bottle until administration in order to avoid unprotected exposure to sunlight. For further details, please refer to HMPL-689 IB and the pharmacy manual.

5.2.2 Drug Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

5.2.3 Drug Accountability

All IP required for this study will be provided by HUTCHMED Limited or contracted Contract Research Organization (CRO). The recipient will acknowledge receipt of the drug by completing and keeping the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

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

Investigational product will be disposed of at the study site according to the study site's institutional standard operating procedure, and the method of destruction must be documented.

5.2.4 Dosage, Administration, and Compliance

The proposed dosage of HMPL-689 is specified in Table 2. Investigational product should be taken at approximately the same times each day. Ideally, doses in the QD cohorts should be taken at 24-hour intervals with ±4-hour window. HMPL-689 can be taken with or without food with approximately 8 ounces (240 mL) of water. The administration time should be accurately recorded in the patient diary.

In the study, patients will not be allowed to make up missed doses; patients will resume dosing at their next scheduled dose.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.3.

Any overdose (Section 6.3.1.6) or incorrect administration of IP should be noted on the patient's source documentation and Case Report Form (CRF). Adverse events associated with an overdose or incorrect administration of IP should also be recorded on the patient's source documentation and Adverse Events page on the CRF (Section 6.3.1.6) and treated according to Section 5.5.

CCI

[redacted]

CCI

[redacted]

5.2.6 Post-trial Access to HMPL-689

Currently, the sponsor does not have any scheduled plans to provide HMPL-689 or any other study interventions after the end of the study or for any patient who has discontinued or withdrawn from the study. The sponsor will evaluate whether to continue providing HMPL-689 after the study is over.

In the event that the sponsor deems post-trial access to HMPL-689 to be appropriate, the sponsor may offer post-trial access to the IP (HMPL-689) free of charge to eligible patients as outlined below.

A patient will be eligible to receive IP after the end of the study if all of the following conditions are met:

- The patient has relapsed/refractory/resistant lymphoma that requires continued IP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive IP after the end of the study if any of the following conditions are met:

- The IP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is accommodated by the patient's insurance or would not otherwise create a financial hardship for the patient).
- The sponsor has discontinued development of the IP or data suggest that the IP is not effective for lymphoma.
- The sponsor has reasonable safety concerns regarding the IP as treatment for lymphoma.
- Provision of IP is not permitted under the laws and regulations of the patient's country.

5.3 Method of Treatment Assignment

Patients will be assigned to dose levels sequentially at dose escalation stage. However, in the dose expansion stage, patients will be allocated based on disease subtype.

5.4 Dose Delays and Modification

Refer to Section 6.8 for recommendations on diagnosis and management of potential toxicities associated with HMPL-689 and/or noted with other PI3Kδ inhibitors. The recommendations provided in Section 6.8 should be evaluated in conjunction with the local clinical standard of care, and overall management plan should be based on the investigator's best clinical judgment.

5.4.1 During Dose Limiting Toxicities Assessment Window

If a patient experiences a DLT, dosing of HMPL-689 will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines. Refer to Section 6.8 for toxicity management recommendations.

Patients who experience a DLT may resume dosing at the same or previous lower dose level at the discretion of the treating physician given that the toxicity is resolved or improved to the baseline level. If a patient experiences an intolerable toxicity at the reduced dose level, he/she will be discontinued from the study treatment. Patient cannot be dose-reduced by more than 2 dose levels. Once reduced, the dose cannot be re-escalated.

No dose reduction in patients without DLT is permitted in the DLT assessment window without the sponsor's approval.

5.4.2 After Dose Limiting Toxicities Assessment Window of Stage 1 or at Stage 2

After DLT assessment window of Stage 1 or at Stage 2, the dose of HMPL-689 may be interrupted if any of the following is observed:

- Any grade pulmonary toxicity
- Any grade diarrhea/colitis
- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia and skin eruption, nausea, vomiting, diarrhea or constipation if well-controlled by systemic or topical medication)

Refer to Section 6.8 for detailed toxicity management recommendations for potential class-related toxicities and dose modification of HMPL-689.

For all other toxicities, treatment with HMPL-689 should be withheld until the toxicity resolves to CTCAE Grade ≤2. Dosing may then be resumed at either the same dose level or the previously evaluated lower dose level if the toxicity is improved to CTCAE Grade ≤2 within 2 weeks, per investigator's discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity of Grade 3 or 4, the dose should be reduced following resolution of the event. If the patient continues to experience intolerable toxicity, a second dose reduction to a previously evaluated lower dose is permitted.

In all cases, every patient is allowed to reduce HMPL-689 dose only twice. If a patient continues to experience intolerable toxicity after 2 dose reductions, or if dosing with HMPL-689 is interrupted for >14 consecutive days due to toxicity (except for those with additional guidance provided in Section 6.8), treatment should be discontinued, unless otherwise agreed by the investigator and the sponsor.

Intra-patient dose escalation to a higher dose level may be permitted by the sponsor provided that the dose level to be escalated has already been cleared at the time of dose increase being proposed.

5.5 Treatment of Overdose

For this study, any dose of study drug greater than the intended daily dose will be considered an overdose (Sections 5.2.4). Procedures for recording overdose events are available in Section 6.3.1.6.

No specific information is available on treatment of overdose of HMPL-689. Nevertheless, in the event of overdose, further HMPL-689 administration should be withheld and subject should be observed closely for clinical features of toxicities. Appropriate supportive treatments should also be provided if clinically indicated.

5.6 Concomitant Therapy and Food

5.6.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to the screening visit to 30 days after the end of treatment or early termination. All such medications should be reported to the investigator and recorded on the Concomitant Medications page of CRF.

Beyond Cycle 1 of Stage 1 or in Stage 2, patients may receive treatment with corticosteroids (at dosages equivalent to prednisone ≤20 mg/day) and/or bisphosphonates for the treatment of bone metastases. Patients may also receive palliative radiotherapy for painful bony metastases. If a patient needs to undergo palliative local radiotherapy to relieve symptoms (such as local radiotherapy to relieve cancer bone pain), the patient may resume administration of the study IP 7 days after the local radiotherapy is over, but should meet the following criteria:

- The patient's radiotherapy-related toxicity has recovered to <Grade 2; and
- The tumor has not progressed.

5.6.2 Prohibited Therapy and Food, and Concomitant Medications Requiring Caution in Use

Patients receiving strong inducers of CYP3A4 or strong inhibitors of CYP3A4 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort) are excluded from the study. Concomitant use of drugs that are known to be strong inducers of CYP3A4 or strong inhibitors of CYP3A4 during the trial should be avoided as far as possible unless considered essential by the investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions.

Drugs that are known to be affected by P-gp should be used with caution.

Appendix 8 provides lists of drugs prohibited and those that should be used with caution. These lists are not intended to be exhaustive, please refer to full prescribing information for all drugs prior to concomitant use with HMPL-689.

Other anticancer agents, investigational agents, and radiotherapy (not for painful bony lesion) should not be given while the patient is during the study.

Corticosteroids are prohibited from 7 days before the date of hematologic screening test to the end of DLT assessment window of Cycle 1 of Stage 1.

Granulocyte colony stimulating factors should not be used prophylactically during the DLT assessment window. Use of prophylactic colony stimulating factors may be considered after Cycle 1 following discussion with the sponsor.

No grapefruit or grapefruit juice or recreational drugs will be allowed during the study.

HMPL-689 shows pH-dependent solubility (i.e., solubility at pH 4.5-6.8 < solubility at pH 1-2) and may be less well absorbed as gastrointestinal pH increases. Patients should avoid using proton pump inhibitors (e.g., esomeprazole, lansoprazole, pantoprazole) during the study. If concomitant use of an acid-reducing agent is unavoidable, H_2-antagonist (e.g., famotidine, ranitidine, nizatidine) may be used but should be administered approximately 10 hours before or 2 hours after HMPL-689 dosing. Antacid may be used, but the antacid dose should be administered at least 2 hours before or 2 hours after HMPL-689 dosing.

5.7 Study Assessments

5.7.1 Definitions of Study Assessments

All patients will be closely monitored for safety and tolerability throughout the study. Continued dosing with HMPL-689 will be offered to patients until disease progression, death, intolerable toxicity, or at investigator's discretion that the patient can no longer benefit from the study treatment, patient withdrawal from the study, or the end of study, whichever comes first.

The schedule of activities is provided in Appendix 1 and the schedule of PK sample collection at dose escalation stage is provided in Appendix 2, the schedule of PK sample collection at dose expansion stage is provided in Appendix 3.

5.7.2 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the study participant before performing any study specific screening tests or evaluations using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and in compliance with country specific regulations and guidelines. One of the original signed ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site within the subject source documentation.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before study treatment. Patients who do not meet the lab testing related eligibility criteria might be re-screened. Re-screening requires re-signing of the ICF and a new screening number will be assigned. Upon implementation of Amendment 5, patients may not be rescreened. The investigator will maintain a screening log to record details of all patients' screened and record reasons for screening failure. Eligibility verification form will be maintained by investigator and confirmed with sponsor prior to initial study treatment.

5.7.3 Medical History and Demographic Data

Medical history and demographic data will be collected at screening. The participant's consent gives the principal investigator, sponsor, sponsor's designees, and regulatory authorities, if applicable, direct access to obtain information from the patient's medical records, including electronic medical records, for the purpose of reviewing information about the participant's health

which is necessary as part of the implementation of the research project as well as for statutory control purposes, including self-regulation, quality control, and monitoring.

Medical history will include clinically significant diseases, surgeries, cancer history (including constitutional symptom/B-symptoms [Unexplained weight loss ≥10% over previous 6 months, fever >38°C/100.5°F for 2 or more weeks without other evidence of infection, night sweats for more than 1 month without evidence of infection]), prior cancer diagnosis (including tumor type, initial diagnosis date, immunohistochemistry, flow cytometry, other pathological findings), prior anti-neoplastic therapies and procedures and related outcome, use of tobacco, use of alcohol and drugs of abuse prior to the screening visit.

Demographic data will include date of birth, sex, and self-reported race/ethnicity.

5.7.4 Concomitant Medication/Concomitant Procedure

Any concomitant medication/procedure within 7 days prior to the screening visit and 30 days after the end of treatment or early termination will be recorded.

5.7.5 Performance Status

The ECOG performance status (Appendix 9) should be assessed by the same study personnel at screening, Days 1 and 15 of Cycle 1, and Day 1 of every cycle from Cycle 2 onwards, and at study completion or early termination, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

5.7.6 Ann Arbor Staging and Rai/Binet Staging

Appendix 10 provides a description of Ann Arbor staging for primary nodal lymphomas.

Appendix 11 and Appendix 12 provide a description of Rai and Binet staging respectively for CLL.

Ann Arbor staging and Rai and/or Binet staging will be collected at screening.

5.7.7 International Prognostic Index

Appendix 13 provides information on the different International Prognostic Indices (IPIs) for the patients with FL, MCL, LPL/WM and other lymphomas. For FL, risk factors refer to Follicular Lymphoma International Prognostic Index (FLIPI). For MCL, risk factors refer to Simplified Mental Cell Lymphoma International Prognostic Index (SMIPI). For LPL/WM, risk factors refer to International prognostic scoring system for Waldenström's macroglobulinemia (ISSWM). For DLBCL and other lymphomas, risk factors refer to IPI.

IPI score will be collected at screening.

5.7.8 Vital Signs

Vital signs will be collected at screening, Days 1, 8, 15, 22 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination, and will include measurements of body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position. The patient should be seated for 5 minutes before the measurement of the blood pressure.

5.7.9 Physical Examination

Physical examination refers to the examination of all body systems, including assessment of head, eyes, ears, nose, larynx, neck, heart, chest, abdomen, limbs, skin, lymph nodes, nervous system, general condition, weight, and height. Physical examination should be performed at screening, Days 1, 8, 15, 22 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination. Weight will be assessed at screening, Day 1 of every cycle from Cycle 2 and onwards, and at study completion or early termination, while height will be assessed only at screening. After screening, a change of physical signs from baseline, and newly presented or patient-reported physical signs should be evaluated. As part of tumor assessment, limited physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, skin lesions, hepatomegaly, and splenomegaly.

5.7.10 Laboratory Assessments

Samples for hematology, chemistry panel, serum amylase and lipase, fasting lipid profile, coagulation, thyroid hormones, hemoglobin A1c, serum β-2 microglobulin, viral serology, urinalysis, leukocyte immunophenotyping and pregnancy testing will be analyzed at the study site's local laboratory. Upon implementation of Protocol Amendment 5, some assessments will no longer be required. Please refer to Appendix 1 for further details.

Laboratory assessments will include the following:

- Hematology consists of complete blood count, including red blood cell count, hemoglobin, hematocrit, reticulocyte count, WBC count with differential (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. Hematology should be tested at screening (within 7 days prior to the first dose of the IP), Days 8, 15 and 22 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination.
- The chemistry panel includes blood urea nitrogen (BUN) or urea, sodium, potassium, magnesium, chloride, calcium, phosphorus, uric acid, fasting glucose, ALT, total and direct bilirubin, AST, alkaline phosphatase (ALP), LDH, protein (total), albumin, creatine phosphokinase, creatinine, and estimated CrCl per Cockcroft-Gault. Chemistry should be tested at screening (within 7 days prior to the first dose of the IP), Days 3, 8, 15 and 22 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination.
- Serum amylase and lipase should be tested at screening (within 7 days prior to the first dose of the IP), Days 8, 15 and 22 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination.
- Fasting lipid profile: includes total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and should be tested at screening (preferably

within 7 days prior to the first dose of the IP), Day 1 of every odd cycle from Cycle 3 and onwards, and at study completion or early termination.

- Coagulation (INR, aPTT, or PT) should be tested at screening (within 7 days prior to the first dose of the IP), Day 1 of every cycle from Cycle 2 and onwards, and at study completion or early termination.
- Thyroid hormones include free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH), and should be tested at screening (preferably within 7 days prior to the first dose of the IP), Day 1 of every odd cycle from Cycle 3 and onwards and at study completion or early termination.
- Hemoglobin A1c should be tested at screening (preferably within 7 days prior to the first dose of the IP), Day 1 of every odd cycle from Cycle 3 and onwards and at study completion or early termination.
- Serum β-2 microglobulin (β2M) should be tested at screening (preferably within 7 days prior to the first dose of the IP), Day 1 of every cycle from Cycle 2 and onwards, and at study completion or early termination.
- Viral serology should be tested at screening and includes the following:
  - HIV
  - HBV (HBsAb, HBsAg and HBcAb)
    - also, HBsAb by enzyme-linked immunosorbent assay and HBV DNA by PCR if the patient is HBcAb positive
  - HCV (HCV antibody)
    - also HCV RNA by PCR if the patient is HCV antibody positive
  - CMV (CMV immunoglobulin G [IgG], CMV immunoglobulin M [IgM])
    - also CMV DNA by PCR if patient is CMV IgG positive
- Urinalysis or dipstick (glucose, protein, ketones, blood), should be tested at screening (within 7 days prior to the first dose of the IP), Day 3 and 15 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 and onwards, and at study completion or early termination. If protein ≥2+ observed during the period of study treatment, a 24-hour urine test should be conducted within 1 week.
- Leukocyte immunophenotyping (Fluorescence-activated Cell Sorting [FACS] subsets) should be done at screening (preferably within 7 days prior to the first dose of the IP), Day 15 of Cycle 1, Day 1 of every cycle from Cycle 2 and onwards, and at study completion or early termination, which includes:
  - Determination of T/B/NK Counts (CD3, CD4, CD8, CD19, CD16/56) using a standard cell marker panel
- Patients with CLL: (optional)
  - Tests of cytogenetic abnormality will be performed at screening (preferably within 7 days prior to the first dose of the IP) for patients with CLL in the dose expansion stage only. These tests should include but not be limited to TP53 mutation, 17p deletion, 11q deletion, 13q deletion, and +12 trisomy.
  - Upon implementation of Protocol Amendment 5, these assessments will no longer be required.
- All women who are not postmenopausal (no menses for 12 months without an alternative medical cause) or surgically sterile will have a serum β-HCG or urine pregnancy test at

screening and at study completion or early termination. In the case of postmenopausal women, the date of menopause onset should be recorded.

- Plasma HMPL-689 concentrations (for PK evaluations) will be assessed using a validated assay. Blood samples should be collected according to the time points in Appendix 2 or Appendix 3.
- Exploratory biomarker assessments will be required for patients in the dose expansion stage and should be collected according to the time points in Appendix 4.
  – Upon implementation of Protocol Amendment 5, this assessment will no longer be required.
- LPL/WM related testing

  – Serum immunoglobulins assessment (quantitative immunoglobulin assessment of IgM, IgA, IgG) will be performed for patients with LPL/WM at screening (preferably within 7 days prior to the first dose of the IP), Day 1 of every cycle from Cycle 2 and onwards, study completion or early termination, quarterly during the extended PFS follow-up period, and at the time of CR confirmation.

5.7.11 Electrocardiogram

All electrocardiograms (ECGs) are required to be performed using a 12-lead tracing. ECG measurements will include PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate.

For dose escalation stage, triplicate ECGs, approximately 2 minutes apart, should be performed at screening, pre-dose, and 2 ± 0.5 and 4 ± 0.5 hours post-dose on Days 1 and 15 of Cycle 1 in order to evaluate concentration-QT relationship with HMPL-689. Single ECG will be conducted at any time on Day 1 of every cycle from Cycle 2 and onwards, and at study completion or early termination. For dose expansion stage, ECGs should be collected according to the schedule and time points in Appendix 3.

Additional ECGs and other cardiac monitoring will be provided as clinically indicated during the study.

5.7.12 Echocardiogram/MUGA

An echocardiogram/multigated acquisition scan (MUGA) to assess left ventricular ejection fraction (LVEF) will be conducted at screening, Day 1 of every odd cycle from Cycle 3 and onwards, and at study completion or early termination. The modality of the cardiac function assessments must be consistent within a patient. For example, if echocardiogram is used for the screening assessment, then echocardiogram should also be used for subsequent scans if required.

5.7.13 Tumor and Response Evaluation

The baseline tumor assessment can be completed within 21 days prior to the first dose of IP (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). All measurable and evaluable lesions should be assessed and documented at screening and each subsequent tumor evaluation, using blood test, physical examination, contrast enhanced CT scans (neck, chest, abdomen, and pelvis) for non-fluorodeoxyglucose (FDG)-avid lymphomas (e.g., LPL/WM, CLL/SLL, and MZL) and/or positron emission tomography(PET)-CT scans for patients with FDG-avid lymphomas

(e.g., FL, MCL, and DLBCL). Enhanced magnetic resonance imaging (MRI) may be used instead of CT scans in patients for whom CT scans are contraindicated.

Tumor assessment will be conducted every 8 weeks (±7 days) for the first 24 weeks and every 12 weeks (±7 days) thereafter. Patients who discontinue HMPL-689 treatment due to reasons other than disease progression will continue tumor assessment according to previous tumor assessment schedule till disease progression, death, end of the study, or start of a new anti-neoplastic therapy, whichever is earlier (see Appendix 1). Upon implementation of Protocol Amendment 5, patients who discontinue HMPL-689 treatment due to reasons other than disease progression will also discontinue from the study.

The same imaging procedure and laboratory tests used to define measurable lesions at baseline should be used throughout the study for each patient.

Bone Marrow Aspirate and Biopsy

A bone marrow biopsy or aspirate is strongly recommended to be done at baseline or up to 3 months before of the Cycle 1 Day 1 and for confirmatory purposes for all patients who achieved a radiologic CR or to confirm suspected progressive disease (PD) based solely upon declines in the platelet count and/or hemoglobin. Upon implementation of Protocol Amendment 5, this assessment will no longer be required.

5.7.14 Timing of Study Assessments

5.7.14.1 Screening and Assessment

All screening evaluations must be completed and reviewed by the investigator and the sponsor's medical monitor to confirm that patients meet all eligibility criteria before the first administration of HMPL-689.

Please see Appendix 1 for the schedule of screening and pre-treatment assessments. Screening and pre-treatment tests will be performed within 21 or 7 days preceding the day of first dose of IP, unless otherwise specified. Results of standard of care tests performed prior to obtaining informed consent and within 21 days prior to study entry may be used; such tests do not need to be repeated for screening.

The baseline tumor assessment can be completed within 21 days prior to the first dose of IP (depending on the patient's disease status a window may be acceptable based on a discussion between the investigator and sponsor's medical monitor). A bone marrow biopsy and aspirate are to be done at baseline or up to 3 months before study treatment.

5.7.14.2 Assessment during Treatment

All visits must occur within ± 3 days (± 1 day during the DLT assessment window) from the scheduled date, unless otherwise noted (Appendix 1). All assessments will be performed on the day of the specified visit unless a time window is specified.

5.8 Participant Completion/Discontinuation

5.8.1 Study Completion/Early Termination Visit

Patients who complete the study or discontinue from the study early will be asked to return to the clinic at 30 ± 7 days after the last HMPL-689 administration for a follow-up visit. Ongoing AEs considered by the investigator to be related to HMPL-689 will be followed up until the event has resolved to baseline, the event is assessed by the investigator as stable, new antineoplastic treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the event.

5.8.2 Extended Progression Free Survival Follow-up

Patients who discontinue HMPL-689 treatment due to reasons other than disease progression will enter the extended PFS follow-up period. During this period, tumor assessment will be conducted quarterly until disease progression, death, the end of the study or the initiation of new antineoplastic therapy, whichever comes earlier. The assessments to be performed at the follow-up visits are listed in Appendix 1. Upon implementation of Protocol Amendment 5, patients who discontinue HMPL-689 treatment due to reasons other than disease progression will also discontinue from the study.

5.8.3 Individual Patient Discontinuation

All study participants have the right to voluntarily withdraw from the study at any time. In addition, the investigator has the right to discontinue a patient from the study at any time. Reasons for withdrawal from the study may include the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or sponsor determines it is in the best interest of the patient
- Non-compliance (e.g., frequently misses doses, visits)

Guidance for diagnosis and management of important potential class toxicities noted on HMPL-689 trials and/or those associated with other PI3Kδ inhibitors is provided in Section 6.8.

The primary reason and date for discontinuation must be recorded appropriately on the CRF.

In addition, stopping rules for individual patients during the dose escalation (Section 5.8.3.1) and dose expansion (Section 5.8.3.2) stages are outlined below.

5.8.3.1 Individual Patient Stopping Rules – Dose Escalation

For specific guidance on the diagnosis and management of important potential class toxicities associated with HMPL-689 and/or other PI3Kδ inhibitors, please refer to Section 6.8.

Dosing will stop for an individual subject, if any of the following occurs:

- A DLT that has not returned to Grade 1 (inclusive) or lower within 14 days, or a DLT that re-occurs in the same subject at a de-escalated lowered dose level
- A DLT equivalent beyond Cycle 1 that has not resolved (even with medical intervention) within 14 days, or that reoccurs after the patient receives a de-escalated lower dose level

5.8.3.2 Individual Patient Stopping Rules – Dose Expansion

For specific guidance on the diagnosis and management of important potential class toxicities associated with HMPL-689 and/or other PI3Kδ inhibitors, please refer to Section 6.8.

- An adverse drug reaction (ADR) severity and its resolution will determine dose interruption, reduction, or discontinuation for an individual
- ADR resolution will determine if subject will discontinue treatment altogether or at the discretion of attending physician, resume treatment at; i) the same dose level, or ii) at a lower dose
- If in professional opinion and recommendation of the PI, individual patients should withdraw from the study
- ADR emerging from drug-drug interaction or food-effect may lead to dose interruption, reduction, or discontinuation

5.8.4 Study Treatment Discontinuation

Patient must discontinue the study treatment in case of:

- Disease progression
- Intolerable toxicity
- Use of new antineoplastic therapy
- Pregnancy with onset during study

The primary reason for study treatment discontinuation should be recorded on the appropriate CRF. Discontinuation from HMPL-689 treatment does not mean discontinuation from the study, and the remaining study procedures should be completed as indicated in the study protocol.

In addition, stopping rules for a cohort or study during dose escalation (Section 5.8.4.1) and dose expansion (Section 5.8.4.2) stages are outlined below.

5.8.4.1 Cohort or Study Stopping Rules – Dose Escalation

There will be no escalation to the next cohort higher dose level until all available data from the current cohort dose level have been reviewed and analyzed by SRC, which will then recommend appropriate dose escalation, de-escalation, or discontinuation. This dose escalation stage will be suspended, interrupted, or discontinued before MTD is attained based on:

- recommendation of SRC
- analysis of emerging PK data, which suggests dose-exposure or target engagement is saturated

At the end of the DLT assessment window for a cohort dose level, safety data will be evaluated to determine either to escalate to the next cohort of higher dose level (Figure 1) or de-escalate to a specific lower dose level (not necessarily pre-specified). The need for dose escalation beyond 50 mg QD, de-escalation to below 5 mg QD, or other regimens, such as BID, will be evaluated and determined by the SRC based on all available cumulative data on safety, PK, pharmacodynamics, and efficacy.

Below are other scenarios that may be applicable:

- One out of 3 patients with DLT will lead to an increase in number of patients on that cohort dose level
- Three out of 6 patients with DLTs will lead to de-escalation to a lower level dose
- Three or more out of 6 patients with DLT at current dose indicate that the dose is unsafe, and that this dose should be de-escalated or discontinued.
- Six out of 6 patients with DLTs at cohort #1 (initial starting dose) may lead to termination of the study arm, amendment of the protocol to reflect a new lower starting dose or changes to inclusion/exclusion criteria, or termination of the entire study.

5.8.4.2 Cohort or Study Stopping Rules – Dose Expansion

The MTD/RP2D of expansion stage 2 will be the dose determined as safe by the SRC based on the conclusion of dose escalation stage 1 section of this phase 1 clinical trial.

The dose or any of the treatment arms/cohorts/tumor types may be re-evaluated for dose interruption, suspension, or reduction based on review of emerging safety data and recommendation of the safety committee.

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[redacted]

5.8.5 Study and Site Discontinuation

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. The sponsor will notify the investigator if the study is placed on hold, or if the sponsor decides to discontinue the study or close any site. If the study is prematurely terminated or suspended, the PI will promptly inform study participants and the Institutional Review Board/Independent Ethics Committee (IRB/IEC). Patients will be contacted, as applicable, and be informed of changes to study visit schedule. Reasons for suspension or termination the study include:

- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/IEC and/or participating regulatory authorities.

5.9 Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Assessment Methods

5.9.1 Pharmacokinetic Assay

Plasma samples will be analyzed to determine concentrations of HMPL-689 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry method. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

5.9.2 Collection Schedule for Pharmacokinetic Samples

NOTE: Upon implementation of Protocol Amendment 5, PK samples for measurement of plasma concentrations of HMPL-689 will not be collected on C3D1 and beyond, and all pharmacodynamic biomarker and pharmacogenetic sample collections will be halted in the dose expansion stage.

Blood samples will be collected at noted time points in the protocol. During the dose escalation stage, the time points for PK blood collection from patients are shown in Appendix 2. During the dose expansion stage, the time points for PK blood collection are shown in Appendix 3.

Time points for pharmacodynamic biomarker collection and pharmacogenetic (PGx) collection are shown in Appendix 4. In this table, the pre-dose PGx blood sample is the only collection for patients in dose escalation and is optional. In the dose expansion, PGx blood samples should be collected in all patients to the extent possible. If, for any reason, the sample is not drawn prior to dosing, it may be taken at any follow-up visit.

After each venous blood sampling, the exact time and dates of blood sampling for PK, pharmacodynamic, and PGx analysis should be recorded on the patient's source documentation and the CRF.

5.9.3 Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Sample Handling and Shipment

Sample handling instructions will be detailed in the Laboratory Manual.

6 ASSESSMENT OF SAFETY

6.1 Safety Plan

HMPL-689 has not been approved for marketing, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with HMPL-689 in completed and ongoing studies. Please refer to the HMPL-689 IB for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs. In addition, guidelines for managing AEs, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Section 5.3.

6.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematologic, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol -specified tests that are deemed critical to the safety evaluation of the IP.

Sponsor or sponsor's designee is responsible for reporting the relevant SAEs to the applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines and local regulatory requirements.

6.2.1 Adverse Event

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 6.3.1.8. Recurrence of an intermittent medical condition (e.g., headache) not present at baseline;
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from IP;
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- Clinical features or clinical sequelae of a suspected overdose of either study drug or a concomitant medication.

6.2.2 Serious Adverse Events

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death);
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death);
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions);
- A congenital anomaly/birth defect in a neonate/infant born to a female patient or female partner of a male patient exposed to the IP;
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

6.2.3 Protocol-Defined Adverse Events of Special Interest Expedited Adverse Events

- Non-serious AEs of special interest are required to be reported by the investigator to the sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 6.3.1 for reporting instructions).
- Adverse events of special interest for this study include: Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 6.3.1.5 and Appendix 14), and non-serious cases of interstitial lung disease/pneumonitis (see Section 6.8, Table 6).
- Please refer to the latest IB for additional information.

6.2.4 Methods and Timing for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 6.2) are recorded on the CRF and reported to sponsor or sponsor's designee in accordance with protocol instructions.

6.2.5 Adverse Event Reporting Period

After informed consent has been obtained but prior to initiation of study medications, only SAEs will be collected.

After initiation of study medications, all AEs and SAEs regardless of causality will be collected until 30 days after the last administration of study treatment or start of a new treatment of anti-neoplasm therapy, whichever is earlier. After this period, investigators should report only SAEs that are related to prior study treatment of HMPL-689 (see Section 6.7).

6.2.6 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 do you feel since your last clinic visit?"

"Have you had any new or changed health problems since last visit?"

6.2.7 Assessment of Severity and Causality of Adverse Events

For guidance on the diagnosis and management of important potential class toxicities noted on HMPL-689 trials and/or those associated with other PI3Kδ inhibitors, please refer to Section 6.8.

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the 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 seriousness (see Section 6.2.2) per seriousness criteria, severity, and causality.

AE should be graded in accordance with NCI CTCAE v5.0. For AE terms not listed in CTCAE v5.0, alternative guideline of AE grading (severity) provided in Table 4 will be used for assessing AE severity.

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP. To ensure consistency of causality assessments, investigators should apply the general guidelines provided in Table 5.

Table 4 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternative Definitions[a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b].
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life--threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
4	Very severe, life threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE	None

ADL = activities of daily living, AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute.
The NCI CTCAE v5.0 can be found at:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to Section 6.2.2.

[a] The alternative definitions will be used for events of Grades 1, 2, 3, and 4 when the observed or reported AE is not in the NCI CTCAE listing.

[b] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 5 Guidance on Causality to the IP

Causality	Guidance
Related	An adverse event will be considered as "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Factors that point toward this assessment include, but are not limited to, a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.
Not Related	An adverse event will be considered as "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event, or the presence of a more likely alternative explanation for the adverse event.

IP=investigational product.

The above guidance should be taken into consideration when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

If an investigator's opinion of "not related to IP" is given for a SAE, another cause of event must be provided by the investigator for the event. If an investigator's opinion of "related to IP" is given for a SAE, the rationale of causality should be provided.

6.3 Procedures for Recording Adverse Events

6.3.1 Recording Adverse Events on the CRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid using colloquialisms and abbreviations.

All AEs (including SAEs) would be recorded on the AE CRF, and the check box for "Serious" would be ticked for entries that fit the criteria of serious. The investigator would also complete an SAE report and submit it to sponsor or sponsor's designee within 24 hours of awareness of the event.

Only one AE term should be recorded in the event field on the CRF.

6.3.1.1 Diagnosis versus Signs and Symptoms

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

6.3.1.2 Adverse Events Occurring Secondary to Other Events

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

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

6.3.1.3 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. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more or less severe, it should also be recorded on the Adverse Event CRF as a new entry.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on an AE/SAE CRF.

6.3.1.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require IP dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc).

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

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

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

6.3.1.5 Abnormal Liver Function Test Results

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin (≥2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo;
2. Among trial patients showing such AT elevations, often with ATs >3 × ULN, one or more patients also show elevation of serum TBL to >2 × ULN, without initial findings of cholestasis (elevated serum ALP);
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Therefore, investigators must report as an AE in the occurrence of either of the following:

- Treatment-emergent ALT or AST ≥3 × ULN in combination with total bilirubin ≥2 × ULN; or
- Treatment-emergent ALT or AST ≥3 × ULN, in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event CRF (see Section 6.3.1.4) and reported to the sponsor's designee as a non-serious AE of special interest (see Section 6.2.3).

The guidance on diagnosis and management of hepatic AEs (including Hy's law) can be found in Section 6.8, Table 8.

6.3.1.6 Overdose

In the event of accidental or intentional overdose, the investigator should inform sponsor study representatives immediately, or no later than 24 hours following the overdose.

- An overdose with associated AEs/SAEs should be recorded in CRF specific module for AE/SAE diagnosis/symptoms.
- An overdose with no associated clinical features should be reported only on study CRF.
- Overdose with no associated clinical features will not be reported as an AE/SAE unless it is an intentional overdose with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

6.3.1.7 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 6.2.5) must have the underlying cause reported to the Sponsor as an SAE, with death listed as the outcome. Deaths that occur during the protocol-specified AE reporting period due to the progression of disease must also be reported to the Sponsor as an SAE. All other on study deaths, regardless of relationship to IP, must be recorded on the Adverse Event CRF and immediately reported to the sponsor (see Section 6.4.1).

Death should be considered an outcome and not a distinct event. The primary event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event CRF. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease (e.g., within 1 hour of the onset of acute symptoms). If the cause of death is unknown and cannot be ascertained at the time of reporting, or if the death was unwitnessed, "unexplained death", "death of unknown cause", or "unwitnessed death" should be recorded on the Adverse Event CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.3.1.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the CRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE/SAE CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

6.3.1.9 Worsening of Lymphoma

Worsening and/or progression of the lymphoma should not be recorded as an AE or SAE, unless the progression directly leads to the patient's death, then the disease progression should be reported as a CTCAE Grade 5 SAE. All worsening and/or progression of the lymphoma data will be captured as efficacy assessment data.

Hospitalization due solely to the progression of underlying lymphoma should not be reported as a serious adverse event. Clinical symptoms of progression may be reported as AEs if the symptom

cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Alternatively, the disease progression is so evident that the investigator may elect not to perform additional disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception, as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being related only to the disease under study, it should be reported as an AE or SAE.

6.3.1.10 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

In addition, hospitalization due solely to the progression of underlying lymphoma should not be reported as a serious adverse event (Section 6.3.1.9).

The following hospitalization scenarios are not considered to be SAEs, but should be reported as AEs instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

6.3.1.11 Pregnancy

If a female patient becomes pregnant while receiving the IP or within 30 days after the last dose of IP, a Pregnancy Report CRF should be reported within 24 hours of learning of the pregnancy to sponsor's Drug Safety Department or sponsor's designee. Pregnancy should not be recorded on the Adverse Event CRF.

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

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the sponsor considers these medically significant), recorded on an Adverse Event CRF, and expeditiously reported to sponsor or sponsor's designee (see Section 6.4.1).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to IP should be classified as an SAE, recorded on the Adverse Event CRF, and expeditiously reported to the sponsor (see Section 6.4.1).

After a patient discontinues study treatment due to pregnancy, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the Sponsor or Sponsor's designee.

6.4 Expedited Reporting Requirements for Serious Adverse Events

Certain events require immediate reporting to allow the sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events on specific reporting forms to the sponsor (see form completion guideline for contact detail) 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 learning of the event, regardless of relationship to IP:

- Serious adverse events (see Section 6.4.2 for further details)
- Non-serious adverse events of special interest (see Section 6.4.2 for further details)
- Overdose
- Pregnancies

6.4.1 Reporting Requirements for All Serious Adverse Events and Protocol-Defined Events of Special Interest

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

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

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/IEC.

6.4.2 Regulatory reporting requirements for Serious Adverse Events

Prompt notification of SAEs by the investigator to sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from sponsor will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.5 Reporting of Dose Limiting Toxicity

Investigators will be required to confirm the presence of DLT for each patient enrolled in the dose-escalation stage of the study within 2 business days after awareness of the event. Investigators will also participate in regular teleconferences with the sponsor's medical monitor, during which they will report any DLTs observed during the DLT observation period for each patient in the dose escalation stage of the study.

6.6 Type and Duration of Follow-Up of Patients after Adverse Events

The investigator should follow all unresolved AEs (including SAEs and DLTs) until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new antineoplastic treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the AE. During the study period, resolution of AEs (with dates) should be documented on the Adverse Event CRF and in the patient's medical record to facilitate source data verification (SDV).

All pregnancies that occur during the study should be followed to determine its outcome.

For some SAEs, the sponsor or sponsor's designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details deemed necessary to evaluate appropriately the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

6.7 Post Study Adverse Events

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify sponsor or sponsor's designee of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if related to prior study treatment. The investigator is not obligated to actively monitor patients for AEs once the trial has ended. Sponsor or sponsor's designee should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study.

6.8 HMPL-689 Dose Modification and Toxicity Management Algorithm for Clinical Trials

This section provides guidance to the investigators for the differential diagnosis and management of the important potential class toxicities noted on HMPL-689 trials and/or those associated with other PI3Kδ inhibitors. This constitutes general recommendations to investigators involved in HMPL-689 studies and should be supplemented with any additional protocol-specific guidance. In case of questions, prompt discussions with the sponsor's clinical representative are recommended. Please see Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12 for the dose modification and toxicity management recommendations for pulmonary AEs (including pneumonia/pneumonitis), diarrhea/colitis, hepatic AEs, infection, neutropenia, thrombocytopenia, and rash and cutaneous skin reactions, respectively.

As a general principle, the recommendations are as follows:

- Differential diagnosis for any adverse event should be diligently evaluated according to standard medical practices.
- Recommendations provided here should be evaluated in conjunction with the local clinical standard of care, and overall management plan should be based on the investigator's best clinical judgment.
- Consultation with specialty medical care is recommended as appropriate and especially prior to any invasive diagnostic or therapeutic procedures.

Table 6 Dose Modification/Toxicity Management Recommendations for Pulmonary Adverse Events Including Pneumonia/Pneumonitis

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 (Asymptomatic, clinical or radiological observations only)	• Educate patient to report any worsening immediately • Monitor for symptoms including SpO2 as clinically indicated. • Request test for CMV-DNA and COVID-19 PCR • Consider pulmonary and/or infectious disease consult, as appropriate	**Consider withholding study drug, as per clinical judgment**	• Re-image within 3 to 4 weeks. Repeat imaging as clinically indicated or for those with radiographic evidence only or with non-infectious pneumonitis • If persistent stable radiologic changes and asymptomatic on 1 to 2 scans, revert to normal restaging scans per protocol • In case of no worsening, study drug may be resumed based on clinical judgment • In any case of worsening, treat as Grade 2, 3, or 4 (see below)
Grade 2 (Symptomatic, mild-to-moderate new or worsening symptoms)	• Educate patient to report any worsening immediately • Monitor for worsening symptoms (e.g., dyspnea/exertional dyspnea) every 3 days or as clinically indicated • Measure SpO2 as clinically indicated • Consider empiric antibiotics while evaluating the differential diagnosis • Request pulmonary and/or infectious disease consult if cause unclear • Evaluate differential diagnosis and causality (infection/immune-related/disease progression) with standard diagnostic tests, including but not limited to the following: o Infectious panel (consider bacterial, viral, and opportunistic infections, including PJP and CMV-use of cultures) o Chest X-ray, SpO2, and HRCT o PFT and BAL, as necessary o ILD markers (KL-6 and SP-D), if available o COVID-19 testing (RT-PCR), if clinically indicated • If determined as infectious, prompt antibiotic, antifungal, or appropriate treatment as per standard guidelines	**Withhold study drug**	• Continue close follow-up and re-imaging and increase steroid dose, as needed • If considered infectious etiology (clearly not immune related): o If resolved in ≤7 days, resume study drug o If resolved in >7 to 28 days, resume study drug at the same or a reduced dose at the discretion of the investigator o If not resolved within 28 days or worsens, consider permanently discontinuing study drug • If considered non-infectious etiology with need for systemic steroid treatment, permanently discontinue study drug o After sustained clinical improvement is observed, gradually taper steroids (e.g., by 5 to 10 mg/week over 4 to 6 weeks) per institutional standards o Patients can be switched to an equivalent/appropriate dose of oral

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
	• If determined as non-infectious (i.e., with immune component), promptly consider systemic steroid treatment o Administer methylprednisolone IV 1 to 2 mg/kg/day or equivalent oral corticosteroid dose		corticosteroids (e.g., prednisone) during the steroid taper. • If etiology unclear and resolves without a need for systemic steroid treatment, then study drug treatment may be restarted at a reduced dose based on investigator's clinical judgment • Monitor closely on restarting treatment; if symptoms recur (at either same or reduced dose), then permanently discontinue the study drug

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up

Grade 3 or Grade 4
 	
(Severe or life-threatening symptoms, new or worsening hypoxia)
	• Hospitalize for further management
	• Request pulmonary and/or infectious disease consult
	• Evaluate differential diagnosis and causality (as described above)
	• Prompt treatment with antibiotic, antifungal, or appropriate treatment as per standard guidelines
	• Prompt treatment with systemic steroids, if considered non-infectious or for suspected immune-related events
	  ○ Administer 1 to 2 mg/kg/day IV methylprednisolone or equivalent
	• Consider bronchoscopy and lung biopsy if clinically indicated
		Withhold study drug	• Continue close follow-up and re-imaging and increase steroid dose, as needed
			• If considered infectious etiology:
			  ○ If resolved to baseline within 28 days, resume study drug at a reduced dose
			  ○ If not resolved within 28 days, permanently discontinue study drug.
			  ○ If worsens or recurs on restarting treatment, permanently discontinue study drug
			• If considered immune-related or non-infectious etiology:
			  ○ Permanently discontinue study drug and treat promptly with steroids (including gradual tapering)
			  – If not improving after 48 hours or worsening, consider additional immunosuppression
			  – After sustained clinical improvement is observed, gradually taper steroids (e.g., by 5 to 10 mg/week over 4 to 6 weeks) per institutional standards
			  – Patients can be switched to an equivalent/appropriate dose of oral corticosteroids (e.g., prednisone) during the steroid taper

BAL = bronchoalveolar lavage; CMV = cytomegalovirus; COVID-19 = coronavirus 2019; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IV = intravenous; KL-6 = Krebs von den Lungen-6; PFT = pulmonary function test; PJP = *Pneumocystis jiroveci* fungus; RT-PCR = real-time polymerase chain reaction; SP-D = serum surfactant protein D; SpO2 = oxygen saturation.

Table 7 Dose Modification/Toxicity Management Recommendations for Diarrhea/Colitis

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 Diarrhea (Mild or moderate, up to 6 episodes per day from baseline, and responsive to antidiarrheal treatment) OR Grade 1 Colitis (Asymptomatic)	• Monitor closely for any worsening of symptoms. Educate patient to report any worsening immediately • Prompt evaluation for etiologies, including infection (with consideration of travel history and COVID-19), dietary factors, and medications, followed by diagnostic testing with stool culture, *Clostridium difficile* testing, CMV, parasite RT-PCR (if available), and COVID-19 testing (as appropriate) • Consider supportive treatment (use of antidiarrheal and IV fluid resuscitation) and dietary optimization	**Continue current dose and reassess in 48 hours**	• Reassess within 48 hours of starting supportive treatment • **If responsive to antidiarrheal treatment:** o **No change in study drug dose** o Monitor as clinically indicated until complete resolution • **If not responsive to antidiarrheal treatment or worsening** o **Withhold study drug** o Manage as per next higher CTCAE grade
Grade 3 Diarrhea (Severe diarrhea, >6 episodes per day from baseline) OR Grade 2 or 3 Colitis (Abdominal pain, mucus or blood in stool, and peritoneal signs)	• Monitor symptoms every 1 to 2 days • Evaluate differential diagnosis and causality (as described above) • Consider GI consult/endoscopy for atypical or refractory cases • Initiate supportive treatment (use of antidiarrheal and IV fluid resuscitation) and dietary optimization • Administer prophylactic antimicrobial or appropriate treatment as per standard guidelines • If determined as non-infectious (i.e., immune mediated), promptly start (including gradual tapering) enteric acting steroids (e.g., budesonide) or systemic steroids such as methylprednisolone IV 1 to 2 mg/kg/day or equivalent	**Withhold study drug**	• Continue close follow-up • Reassess within 48 hours of starting supportive treatment o **If resolves to Grade 1 or baseline with antidiarrheal treatment, restart study drug at the same dose level** • **If considered infectious etiology (clearly not immune related):** o **If resolves to Grade 1 or baseline in <28 days, resume study drug at the same or a reduced dose at the clinical judgment/discretion of the investigator** • **If considered non-infectious etiology with need for systemic steroid treatment, then permanently discontinue study drug** o After sustained clinical improvement is observed, gradually taper steroids (e.g., by 5 to 10 mg/week over 4 to 6 weeks) per institutional standards

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
			○ Patients can be switched to an equivalent/appropriate dose of oral corticosteroids (e.g., prednisone) during the steroid taper • **If etiology unclear and resolves without a need for systemic steroid treatment, then study drug treatment may be restarted at a reduced dose based on investigator's clinical judgment** • **Monitor closely on restarting treatment; if symptoms recur at Grade 3 or higher, permanently discontinue the study drug**
Grade 4 Diarrhea or Colitis (Life threatening)	• Hospitalize and promptly start supportive treatment. • Consider endoscopy and GI consult, as needed • Evaluate differential diagnosis and causality (as described above) • Prompt treatment with systemic steroids such as 1 to 2 mg/kg/day IV methylprednisolone or equivalent and/or empiric antibiotics	**Permanently discontinue study drug**	• Continue close follow-up until resolution • If improves to baseline, gradually taper steroids (e.g., by 5 to 10 mg/week over 4 to 6 weeks) per institutional standards • If refractory to steroids, consider other immunosuppression (as clinically indicated)

CMV = cytomegalovirus; COVID-19 = coronavirus 2019; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; IV = intravenous; RT-PCR = real-time polymerase chain reaction.

Table 8 Dose Modification/Toxicity Management Recommendations for Hepatic Adverse Events

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 AST/ALT elevation (≤5 times upper limit of the normal [ULN] or from baseline, if baseline is abnormal)	• Evaluate differential diagnosis and causality (including pre-existing liver disease and infectious etiology including possible COVID infection [use RT-PCR for diagnosis]) • Close monitoring for worsening of any clinical signs/symptoms (e.g., hyperbilirubinemia) • Close monitoring of transaminase and bilirubin levels until return to Grade 1 or <3 times ULN • Manage with supportive care for symptom control • If the AST/ALT and bilirubin levels meet the definition of Hy's law, permanently discontinue the study drug	**Continue current dose**	• If likely immune mediated, seek hepatic consult and consider use of steroids as clinically indicated • In case of worsening, treat as Grade 3 or 4

Grade 3 AST/ALT elevation (>5 to 20 times ULN or from baseline, if baseline is abnormal)	• Evaluate differential diagnosis and causality (including pre-existing liver disease and infectious etiology)
	• Close monitoring for any clinical symptoms
	• Weekly monitoring of transaminase and bilirubin levels until return to Grade 1 or <3 times ULN
	• Consider hepatic consult and treat accordingly per standard treatment guidelines
	• Permanently discontinue study drug if the patient meets the definition of Hy's law
	  ○ AST or ALT value > 3 × ULN and TBL > 2 × ULN
	  ○ No other reason to explain combination of increased AST or ALT and TBL, ALP normal (i.e., no initial findings of cholestasis)
		Withhold study drug	• **If resolved to Grade 1 or baseline in less than 28 days, resume study drug at the same or a reduced dose at the discretion of the investigator**
			• **If not resolved to Grade 1 or baseline more than 28 days or worsens or recurs after re-initiating therapy, permanently discontinue study drug**
			• If likely immune mediated, seek hepatic consult and consider use of steroids with gradual taper

Grade ≥4 (>20 times ULN or from baseline, if baseline is abnormal)	Evaluate differential diagnosis and causality (including pre-existing liver disease and infectious etiology) Consider hepatic consult and treat accordingly per standard treatment guidelines If the AST/ALT and bilirubin levels meet the definition of Hy's law, permanently discontinue the study drug	**Permanently discontinue study drug**	• Continue close follow-up until resolution • If likely immune mediated, seek hepatic consult and consider use of steroids with gradual taper

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = coronavirus 2019; CTCAE = Common Terminology Criteria for Adverse Events; RT-PCR = real-time polymerase chain reaction; TBL = total bilirubin level; ULN = upper limit of normal.

Table 9 Dose Modification/Toxicity Management Recommendations for Infection

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 Infection	• Evaluate differential diagnosis and causality (infection/immune-related/disease progression) with standard diagnostic tests (including but not limited to imaging, COVID-19 testing, chest X-ray, cultures, etc) • Consider supportive care, including use of growth factors for patients with persistent or severe myelosuppression • Once confirmed as infection, treat as per standard guidelines (including but not limited to antibiotics or antifungals) • Consider infectious disease consult, as appropriate • For patients with pulmonary or GI toxicities or myelosuppression, also refer to guidelines for management of those conditions	**Continue current dose**	• In case of persistent infection or worsening, manage as next higher grade
Grade ≥3 Infection	• Evaluate causality and consider supportive care and/or anti-microbial therapy as described above • Obtain infectious disease consult	**Withhold study drug**	• **If resolved to baseline within 28 days, resume study drug at the same or a reduced dose at the discretion of the investigator** • **If not resolved within 28 days or worsens or recurs on restarting treatment, permanently discontinue study drug**
Clinical CMV infection or reactivation or viremia (Positive PCR or antigen test)	• In case of symptomatic CMV viremia or end-organ damage (such as hepatitis, colitis, pneumonitis, or retinitis) or CMV reactivation, promptly start appropriate antiviral treatment (such as ganciclovir or valganciclovir) • If asymptomatic, with CMV RNA >100,000 copies or CMV levels increasing over multiple measurements, withhold study treatment. Consider antiviral treatment with guidance from infectious disease consult	**Withhold study drug**	• Monthly monitoring for CMV reactivation by PCR or antigen test • **In case of symptomatic CMV viremia or end-organ damage (such as hepatitis, colitis, pneumonitis, or retinitis) or CMV reactivation, permanently discontinue study treatment**
Pneumocytis jiroveci infection	• Consider pulmonary consult and bronchoscopy. Start empiric treatment (also refer to management of pulmonary toxicities [Table 6])	**Withhold study drug**	• In case of PJP diagnosis, permanently discontinue study treatment.

CMV = cytomegalovirus; COVID-19 = Coronavirus 2019; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; PCR = polymerase chain reaction; PJP = *Pneumocystis jiroveci* infection; RNA = ribonucleic acid.

Table 10 Dose Modification/Toxicity Management Recommendations for Neutropenia

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 Neutropenia (ANC of ≥1 × 10^9/L)	• Monitor for any fever • If persistent, consider supportive care as needed	**Continue current dose**	• In case of worsening of neutropenia or neutropenic fever, treat as Grade 3 or 4
Grade 3 Neutropenia (ANC of 0.5 to 1 × 10^9/L)	• Monitor with complete blood count every 2 weeks • Consider supportive care, including use of growth factors for patients with persistent or severe myelosuppression • If persistent Grade 3, recurs or worsens, withhold study drug	**Continue current dose**	• **On resolution to a lower grade or baseline, resume at the same dose level** • **In case of recurrence after restarting treatment, consider next lower dose level at the discretion of the investigator** • In case of worsening of neutropenia or neutropenic fever, treat as Grade 4
Grade 4 Neutropenia (ANC of <0.5 × 10^9/L) OR Occurrence of neutropenic fever or infection	• Monitor with complete blood count at least every 2 weeks • Strongly recommend initiation of growth factors and other supportive care including antibiotic prophylaxis	**Withhold study drug**	• **On resolution to a lower grade or baseline (ANC of ≥1 × 10^9/L), resume at the same dose level or at the next lower dose level at the discretion of the investigator (also refer to treatment guidelines for infection)** • **In case of recurrence after restarting treatment, resume at the next lower dose level**

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events.

Table 11 Dose Modification/Toxicity Management Recommendations for Thrombocytopenia

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade ≤3 Thrombocytopenia without bleeding (Platelet count >25 × 10^9/L)	• If persistent, consider supportive care as needed	**Continue current dose**	• In case of bleeding or worsening, manage as next higher grade
Grade 4 Thrombocytopenia (Platelet count <25 × 10^9/L) OR Any grade thrombocytopenia with bleeding	• Monitor with complete blood count at least every 2 weeks • Consider supportive care including platelet transfusion (as clinically indicated) • On resolution to a lower grade or baseline, resume at the same dose level	**Withhold study drug**	• **In case of recurrence after restarting treatment, consider next lower dose level at the discretion of the investigator**

CTCAE = Common Terminology Criteria for Adverse Events.

Table 12 Dose Modification/Toxicity Management Recommendations for Rash and Cutaneous Skin Reactions

Adverse Reaction CTCAE V5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 Rash or Cutaneous Reactions (covering <30% of BSA, with no evidence of superinfection)	• Initiate supportive treatment with emollients, antihistamines (for pruritus), or topical steroids • Counsel patients to avoid skin irritants and sun exposure • Monitor closely for any worsening	**Continue current dose**	• In case of worsening, treat as Grade 3 or 4
Grade 3 Rash or Cutaneous Reactions (covering >30% BSA, moderate/severe symptoms, associated with local superinfection)	• Initiate supportive treatment with emollients, antihistamines (for pruritus), or topical steroids • If rash doesn't resolve with topical steroids, consider low dose systemic steroids (0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent per institutional guidelines) • Monitor closely for any worsening • Consider skin biopsy and dermatology consult	**Withhold study drug**	• **If resolved in less than 28 days, resume study drug at the same or a reduced dose as per investigator's discretion** • **If not resolved within 28 days, permanently discontinue study drug. Treat as the next higher grade**
Grade ≥4 (Life threatening) OR Any grade of SJS, TENS, or DRESS	• Obtain skin biopsy and dermatology consult • Treat as per the diagnosis and standard treatment guidelines (such as IV antibiotics and IV steroids)	**Permanently discontinue study drug**	• Continue close follow-up until resolution • If improves to baseline, gradually taper steroids as per local standard

BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; DRESS = drug reaction with eosinophilia and systemic symptoms; IV = intravenous; SJS = Steven's Johnsons' Syndrome; TENS = toxic epidermal necrolysis.

7 STATISTICAL ANALYSIS

7.1 Determination of Sample Size

CCI . In general, the maximum sample size in the dose-escalation stage will be determined by sponsor and investigator based on the accumulated safety data and the mTPI-2 design (Ji 2013). CCI .

Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than DLT or receive less than 75% of assigned study medication during DLT assessment window will be replaced. This may result in the actual enrollment exceeding the planned enrollment.

CCI

7.1.1 Stage 1: Dose Escalation Stage

The maximum sample size at mTPI2 for this stage will be determined by sponsor and investigator based on the accumulated safety data and mTPI-2 design (Ji 2013). The maximum sample size under the mTPI-2 method is $k \times (d + 1)$, where k denotes the cohort size and d denotes the number of doses. The minimum cohort size in this study is 3 patients per cohort. To ensure that the highest dose (if needed) is reached per the mTPI-2 design and the availability of additional cohorts, it is estimated that approximately CCI patients will be needed in this study.

7.1.2 Stage 2: Dose Expansion Stage

CCI

CCI

[redacted]

CCI

[redacted]

7.2 Analysis Populations

The following analysis populations are defined for the study:

Full Analysis Set (FAS):

The FAS is defined as all patients who receive at least one dose of HMPL-689. The FAS will be used for analysis of safety data and efficacy endpoint PFS.

DLT Evaluable Analysis Set: All patients enrolled in the dose escalation phase of the study who are evaluable for DLT assessment. A subject is DLT evaluable if he/she meets the following criteria:

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

OR

– has not completed the DLT assessment period due to a DLT

Efficacy Analysis Set (EAS):

All patients who receive at least one dose of HMPL-689 and have a baseline tumor assessment and at least one post-baseline assessment will be considered evaluable for anti-tumor efficacy endpoints such as ORR, clinical benefit rate (CBR), TTR, and DoR.

Pharmacokinetics Analysis Set (PKAS):

The PKAS is defined as all patients who received at least one dose of HMPL-689 and have at least one PK sample obtained and analyzed.

7.3 Statistical Methods

Data will be summarized by dose level, subtype of malignancy and for overall as appropriate. Continuous assessments will be summarized by number of patients (n), mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include the number and percentage of patients for each category.

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

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

7.3.1 Disposition of Patients Enrolled in the Study

The patient disposition in the dose escalation and dose expansion stages will be summarized for each dose level.

Study drug administration data will be listed by dose level. The total duration of exposure, dose intensity, and relative dose intensity of HMPL-689 will be summarized by descriptive statistics.

7.3.2 Safety Analysis

Safety parameters, including study drug exposure, DLTs, recorded TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG parameters and physical examination findings, will be summarized by dose level across different stages for the FAS.

7.3.2.1 Dose Limiting Toxicities

All DLTs will be listed.

7.3.2.2 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the corresponding intensity will be graded according to NCI CTCAE v.5.0. Analysis of AEs will be performed for TEAEs, which are defined as AEs that onset or worsen in severity on or after the first dose of HMPL-689. All TEAEs will be summarized in frequency and percentage of patients for each dose level.

The same analysis will be performed for SAEs, study drug–related TEAEs assessed by the investigators, TEAEs leading to dose adjustment, or treatment discontinuation, and AEs of special interest.

7.3.2.3 Clinical Laboratory Test Values

Descriptive statistics for each clinical laboratory test will be presented for each dose and scheduled visit. Laboratory test values from the hematology and chemistry panels, which are gradable in NCI CTCAE, will be summarized by the shift of NCI CTCAE grade from baseline to the worst grade on study treatment period.

Selected laboratory tests will be plotted over time for each patient. All laboratory test results will be listed.

7.3.2.4 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature) will be summarized with descriptive statistics by dose level and visit.

Selected vital signs tests will be plotted over time for each patient. All vital sign data will be listed.

7.3.2.5 12-Lead ECGs

Descriptive statistics for ECG parameters (PR interval, QRS interval, RR interval, QT interval, QTcF interval [QT interval/cube root of RR interval], and heart rate) will be presented by dose level and visit. Refer to Section 7.3.5 for further details.

7.3.2.6 Physical Examination

All physical examination findings will be listed.

7.3.3 Pharmacokinetic Analysis

Pharmacokinetic parameters will be analyzed with the PKAS. A non-compartmental model analysis will be performed for plasma concentration data from the escalation stage using Phoenix WinNonlin. Individual and mean plasma concentration of HMPL-689 versus time data will be tabulated and presented. The individual and mean PK parameters determined following analysis of the concentration of HMPL-689 versus time data, will include, but are not limited to AUC, C_{max}, T_{max}, C_{min}, CL/F and AR. N, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [%CV] will be presented. The actual times of plasma sample collection will be used in the determination of the PK parameters. Individual and mean HMPL-689 concentrations will be plotted by dose level. Details of the PK analysis, including data handling rules and software used to perform the PK analysis, will be provided in the PK analysis plan (PKAP).

Plasma concentration data of HMPL-689 from the expansion stage will be tabulated and presented as described in the PKAP.

7.3.4 Efficacy Analysis

Efficacy endpoints will be summarized by dose level for each type of malignancy.

The best percent change from baseline (%) in the target lesion, ORR, CBR, and the corresponding 95% CI based on Clopper-Pearson method will be presented by dose level.

The PFS, TTR, and DoR will be summarized with Kaplan-Meier (KM) method if data permit, and the corresponding KM curve will be plotted.

ORR, CBR, PFS, TTR, and DoR data will be listed for all patients.

Tumor assessment in different types of malignancies will be evaluated according to specified guidelines/criteria:

- CLL: the modified International Workshop on CLL guideline (Hallek 2008, Cheson 2012), see Appendix 5.
- LPL/WM: consensus of international workshops on WM (IWWM-7 consensus) (Dimopoulos 2014), see Appendix 6.
- Other lymphomas: Lugano Response Criteria for Hodgkin and NHL (Cheson 2014), see Appendix 7.

In the evaluation of the tumor response endpoints (ORR, TTR, CBR, DoR, and PFS), the investigator-assessed data will be utilized for tumor assessment.

7.3.5 Pharmacodynamics (Electrocardiogram) Analysis

Patients who 1) receive at least 1 dose of study drug and 2) have baseline and at least 1 postdose ECG measurement will be evaluable for pharmacodynamic (ECG) evaluation. Patients who had reduced dosage, prolonged dose interruption of >2 days in cycle 1, any dose interruption within 3 days before Cycle 1 Day 15, or were discontinued from the study prior to the completion of ECG data collection (Cycle 1 Day 15) will be excluded. For each of the ECG parameters, the average values from the 3 readings of a triplicate ECG set will be used in the analysis.

For all ECG parameters, the baseline will be defined as the mean values of the triplicate ECG measurements taken at predose on Cycle 1 Day 1.

7.3.5.1 Corrected QT Intervals

The terminology QTc is used in this section as a general notation for QTc using any of the specified methods.

The QT interval data will be corrected for heart rate using 2 correction methods (QTcF and corrected QT interval by Bazett – QTcB). For each QTc correction method, the relationship between QTc and RR at baseline will be evaluated graphically by plotting the logarithm of baseline QTc values against the logarithm of corresponding RR intervals. QTcF will be used as the primary correction method for statistical analysis. If the correlation between QTc and RR intervals remains significant using the Fridericia correction method, an alternative correction method may be considered for statistical analysis in addition to QTcF.

For the statistical analysis based on the primary correction method (QTcF), the mean changes from baseline (ΔQTc) at each time point will be summarized (mean, standard deviation, median and

range, and 2-sided 90% CI). Mean values for the difference and 2 sided 90% CI for mean difference will be calculated at each time point.

The primary analysis will focus on the maximum mean change from baseline in QTc (ΔQTc) on Cycle 1 Day 15, which will be estimated by the mean QTc change at around t_{max}, the time when the C_{max} is reached (i.e., steady state). The same analysis will be performed for ΔQT data using other correction methods if data warrant. The mean change from baseline in QTc (±standard deviation) over time will be plotted.

In addition, QTc will be categorized based on International Council for Harmonisation (ICH) E14 guidelines. Tables will present the number and percentage of patients meeting or exceeding the following categories:

- QTc prolongation:
  - Absolute values >450 to ≤480 msec
  - Absolute values >480 to ≤500 msec
  - Absolute values >500 msec
- QTc change from baseline:
  - Increase from baseline >30 to ≤60 msec
  - Increase from baseline >60 msec

7.3.5.2 Heart Rate, QRS, and PR Intervals

For each treatment and time point of measurement, heart rate, QRS interval, and PR interval, as well as the change from baseline in heart rate, QRS, and PR (Δheart rate, ΔQRS, ΔPR), will be summarized using descriptive statistics (mean, standard deviation, median, range, and 90% CI). The number and percentage of patients with heart rate >100 bpm will be tabulated for each time point. The number and percentage of patients with QRS >110 msec will be tabulated for each time point. The number and percentage of patients with PR >200 msec will be tabulated for each time point.

7.4 Interim Analysis

There is no interim analysis planned for this study.

8 ETHICS

8.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/IEC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the sponsor or sponsor's designee, investigators are required to report to their respective IRB/IEC promptly all unanticipated problems involving risk to human patients. Some IRBs/IECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.3 Patient Information and Consent

The investigator or his/her representative, qualified by education, training, and experience to comply with GCP and applicable regulatory requirements, will provide verbal and written information to the patient explaining the nature of the study, and answering all questions. Prior to any study-related screening procedures being performed on the patient, the informed consent statement will be reviewed, signed, and dated by the patient and the person who administered the informed consent. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. A copy of the informed consent form will be given to the patient and the original will be placed in the patient's medical record and must be available for verification by study monitors at any time. If applicable, it will be provided in a certified translation of the local language.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. Signed and dated Informed Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

8.4 Data Privacy and Confidentiality

The investigator and the sponsor or its designee must observe and adhere to any country data privacy laws and regulations (including country specific Data Protection Acts). 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. Appropriate consent for participation and understanding of the use and disclosure and/or transfer (if applicable) of protected information and research samples must be obtained.

Subject names will not be supplied to the sponsor or its designee. The sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any sponsor location. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the CRF, where permitted; if the patient's name appears on any other document (eg, laboratory report), it must be de-identified before submitting to the sponsor or its designee.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that data generated by this study must be available for inspection upon request by representatives of the China FDA and other national and local health authorities, study monitors, representatives, and collaborators, and the IRB/IEC for each study site, as appropriate and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

9 STUDY DOCUMENTATION, CASE REPORT FORM, AND RECORDS

9.1 Source Data Documentation

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. These include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, Xrays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the CRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the sponsor direct access to applicable source documents and reports for trial-related monitoring, sponsor audits, and IRB/IEC review. The investigational site must also allow inspection by applicable regulatory authorities.

9.2 Use of Computerized System

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the CRFs can be verified.

9.3 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the IP. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of HUTCHMED Limited. Written notification should be provided to HUTCHMED Limited for transfer of any records to another party or moving them to another location.

10 MONITORING

Site visits will be conducted by an authorized designee of HUTCHMED Limited to check study data, patients' medical records, and CRFs. The Principal Investigator will permit study monitors/sponsor's representatives and collaborators other regulatory agencies, IRBs/IECs, and the respective national or local health authorities to inspect facilities and records relevant to this study.

It will be the study monitor's responsibility to check the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The study monitor must verify that the patient received the IP assigned by the dose level. The study monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator (or designee) agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11 DATA MANAGEMENT

11.1 Data Quality Assurance

The overall procedures for quality assurance of clinical study data are described in the sponsor or CRO standard operation procedures. Sites will be responsible for data entry into the electronic data capture (EDC) system. Accurate and reliable data collection will be assured by verification and crosscheck of the CRFs against the investigator's records by the study monitor. In the event of discrepant data, the CRO will request data clarification from the sites. Sponsor and CRO will be responsible for the data management of this study, including quality checking of the data.

11.2 Electronic Case Report Forms

Electronic data capture (EDC) will be used for this study, meaning that all CRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized site staff designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized site staff prior to the study being initiated and any data being entered into the system for any study patients.

The study monitor will review the CRFs and evaluate them for completeness and consistency. The CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. All corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with the time and date will be logged. If additional corrections or clarifications are needed, the responsible study monitor or data manager will raise a query in EDC. The appropriate investigational staff will answer queries. This will also be audit trailed by the EDC.

The investigator is responsible for maintaining source documents. These will be made available for audit or inspection. The investigator must submit a completed CRF for each patient who has been screened. All supportive documentation submitted with the CRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique User ID. The Investigator must ensure all data entries in the CRF are accurate and correct and will be required to sign off electronically on the clinical data. This will be facilitated by means of the investigator's unique user ID and password. If an entry on a CRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

At the end of the study, the investigator will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records.

11.3 Coding

Adverse events, medical history/surgery, concomitant procedure will be coded using MedDRA. Concomitant medications, anti-neoplastic medication of post-IP and pre-IP will be coded using World Health Organization-Drug Dictionary (WHO-DD).

12 USE OF INFORMATION AND PUBLICATION

12.1 Use of Information

All information regarding HMPL-689 and HUTCHMED Limited's operations, such as HUTCHMED Limited's patent applications, formulae, manufacturing processes, basic scientific data, or formulation information, supplied by HUTCHMED Limited and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by HUTCHMED Limited in connection with the development of HMPL-689. This information may be disclosed as deemed necessary by HUTCHMED Limited or its designee to other clinical investigators, other pharmaceutical companies, and to the regulatory agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide HUTCHMED Limited with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

The investigator will maintain a confidential patient identification code list of all patients enrolled in the study (by name and patient number). This list will be maintained at the site and will not be retrieved by HUTCHMED Limited or its designee.

12.2 Publication

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice (see "International Committee of Medical Journal Editors authorship requirements" http://www.icmje.org/), the sponsor will generally support publication of multicenter trials only in their entirety and not as individual center 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. Any formal publication of the study in which contribution of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel.

HUTCHMED Limited agrees that before it publishes any results of this study, it shall provide the investigator a pre-publication manuscript for review at least 30 days prior to the submission of the manuscript to the publisher.

The investigators have the right to publish the results of the study, but with due regard to the protection of confidential information. Accordingly, HUTCHMED Limited shall have the right to review and approve any paper for publication, including oral presentation and abstracts, which utilize data generated from this study. At least 30 days before any such paper or abstract is presented or submitted for publication, a complete copy shall be given to HUTCHMED Limited for review. HUTCHMED Limited shall review any such paper or abstract and give its comments to the author(s) promptly. The investigator shall comply with HUTCHMED Limited' confidential information in any such paper and agrees to withhold publication of the same for an additional 30 days in order to permit HUTCHMED Limited to obtain patent or other proprietary rights protection, if HUTCHMED Limited deems it necessary.

This confidential information shall remain the sole property of HUTCHMED Limited, shall not be disclosed to others without the written consent of HUTCHMED Limited, and shall not be used except in the performance of this study.

It is understood by the investigator that the information developed in the clinical study will be used by HUTCHMED Limited in connection with the development of HMPL-689 and, therefore, may be disclosed as required to other clinical investigators, other pharmaceutical companies, or to regulatory agencies. It is understood that there is an obligation to provide HUTCHMED Limited with complete test results and all data resulting from this study and to provide direct access to source data/documents for study related monitoring, audits, IRB/IEC review, and regulatory inspection.

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Approval Task	PPD 12-Dec-2022 13:13:43 GMT+0000

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