A Phase I, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-523 in Patients with Relapsed or Refractory Lymphoma

Investigational Product(s)	HMPL-523 CCI Tablets
Protocol Number	2018-523-00US1
Clinical Phase	Phase I
Amendment	5
Sponsor	HUTCHMED Limited Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone Shanghai, China, 201203
Clinical Trial Registry Identifiers	ClinicalTrials.gov Identifier: NCT03779113 EudraCT Identifier: 2018-004807-38 EU (CTIS) Study Number: 2024-515123-11-00 IND Number: 129706
Issue Date	14 June 2024

Confidentiality Statement

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with this clinical study protocol, Good Clinical Practices as outlined by International Council for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. At the final release of ICH E6(R3), this study shall immediately comply with the new regulation. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

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

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

All personnel involved in the conduct of this study have completed human subject's protection and Good Clinical Practice training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Phase I, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-523 in Patients with Relapsed or Refractory Lymphoma
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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]	**Title:**
PPD	Executive Vice President, Head of Research and Development, and Chief Medical Officer HUTCHMED International Corp.
Signature: *See appended signature page.*	**Date:** [DD Month YYYY]

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study 2018-523-00US1 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 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 [Last name, first name]	**Title** [Title at institution]	**Institution** [Address]

Signature	**Date** [DD Month YYYY]

DOCUMENT HISTORY

Amendment	**Date**
Original Protocol	11 October 2018
1	09 April 2020
2	07 August 2021
3	23 July 2022
4	12 December 2022
5	14 June 2024

AMENDMENT SUMMARY

Protocol 2018-523-00US1 Amendment 5 replaces Protocol 2018-523-00US1 Amendment 4. Protocol Amendment 5 is considered a substantial modification based on the criteria set forth in Article 2, 2 (13) of Regulation (EU 536/2014) of the European Parliament and the Council of the European Union.

This amendment now incorporates additional detail to facilitate transition of this study to the new EU Clinical Trial Regulation (EU 526/2014) and upcoming ICH E6(R3) release.

The primary purpose of Amendment 5 is to update the "end of study" definition from 1 year after the last patient's first visit to 2 years after the last patient's first visit. This is intended to provide additional duration on treatment for patients who are deriving clinical benefit on HMPL-523 treatment. The new end of study definition will be the "date on which all patients have their last visit or 2 years after the last patient has his/her first visit, whichever comes first."

This study is closed to new enrollment; the last patient was enrolled on CCI Currently enrolled patients who are deriving clinical benefit from treatment with HMPL-523 may continue to participate in the study as per the protocol. 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 18.

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.
Section 4.1 Description of Study	Added the following statement: "The start of the clinical study is defined as the date the study is open for recruitment at any site. This date was 21-Feb-2019. The start of the clinical study in Europe is defined as the date the clinical study is open for recruitment at the first clinical study site within an EU Member State. This date was 05-Sep-2019."	To comply with necessary requirements for studies conducted in European Union (EU) Member States.
Synopsis, Section 4.5 Dose Expansion Stage (Stage 2), Table 2 Dose Expansion Cohorts; Section 7.1 Determination of Sample Size	Language was added to indicate that as of Amendment 5, the study will be closed to new enrollment and to update the numbers in Table 2 to reflect the number of patients enrolled as of Amendment 4 and number continuing in the study as of Amendment 5.	The sponsor has discontinued development of the study drug for lymphoma in the specific region and has closed the study for further enrollment.
Synopsis, Section 4.6 End of Study	Language was updated to change the end of study definition from 1 year to 2 years after the last patient's first visit.	Patient-centric decision to extend the study to allow for additional duration of therapy.
Section 5.1.1 Inclusion Criteria, Criterion #4	Updated to include that the study is now closed to enrollment	Updated to include that the study is now closed to enrollment.

Section Number	Summary of Change	Rationale for Change
Section 5.3.5 Post-Trial Access to HMPL-523	Added language to reflect the sponsor has discontinued development of the study drug for lymphoma in the specific region	Updated language to reflect that sponsor has discontinued development of study drug for lymphoma in the specific region.
Section 5.4.3 Recommendations for Management of Toxicity Including Dose Modification	Added the following statement: "Approved prescribing information for other drugs used to treat relapsed or refractory lymphoma should be utilized to guide management of toxicities associated with these drugs."	To comply with necessary requirements for studies conducted in EU Member States.
Section 5.6.2 Informed Consent Forms and Screening Log	Added the following statement: "If the subject cannot sign the ICF (eg, due to an inability to read or write), a legally acceptable representative of the subject must sign the ICF. If the subject and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the subject and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the subject and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations."	To comply with necessary requirements for studies conducted in EU Member States.
Section 5.6.9 Laboratory Assessments, Appendix 1 Schedule of Activities	Updated language to reflect that leukocyte immunophenotyping will not be performed from Cycle 3 onwards	To reduce patient burden.
Section 5.6.10 Electrocardiogram, Appendix 1 Schedule of Activities	Updated language to reflect that electrocardiograms will not be performed from Cycle 3 onwards unless clinically indicated	To reduce patient burden.
Section 5.6.12 Tumor and Response Evaluation	Updated language reflecting that tumor assessment will be performed quarterly for those who discontinue the drug due to reasons other than disease progression.	Amended to provide clarity on imaging assessment for these subject
Section 5.8 Study/Site Discontinuation and Closure	Added bullet "Sponsor decision to discontinue clinical development of the drug in the specific indication or in the specific region."	To expand on Sponsor decision regarding clinical development of study drug.
Section 5.9.1 Collection Schedule, Appendix 3 Pharmacokinetics and Pharmacodynamics Sampling Time Points (Dose Expansion Stage)	Pharmacokinetic (PK)/pharmacodynamic collection schedule updated to reflect that as of Amendment 5, PK samples for measurement of plasma concentrations	To reduce patient burden.

Section Number	Summary of Change	Rationale for Change
	of HMPL-523 and [redacted] will not be collected on Cycle 5 Day 1 and beyond in the dose expansion stage. Also, dose modification language was removed.	
Section 6.2.2 Serious Adverse Events	Added paragraph "All SAEs will be followed until resolution, stabilization, event is otherwise explained, or participant is lost to follow-up. Depending on the event, follow-up may require additional tests or medical procedures as indicated and/or referral to a general physician or a medical specialist. All pregnancies that occur during participation in the study should be followed to determine the outcome of the pregnancy."	To comply with necessary requirements for clinical studies conducted in EU Member States.
Section 8.2 Ethical Conduct of the Study	Added EU regulation number 536/2014	To comply with necessary requirements for studies conducted in EU Member States.
Section 9.3 Retention of Records, Appendix 17 (new)	Changed required storage time of records from "2 years after the study is completed" to "25 years after the study is completed or longer if mandated by local regulatory requirements." Added language to clarify accurate recording of source data and documents, investigator responsibility in recording the study, and storage at study site or approved storage facility. Added the following statement: "Subject medical files will be archived in accordance with national law." Modified the following statement: "The Sponsor will store the study documentation for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; at least 2 years have elapsed since the formal discontinuation of clinical development of HMPL-523; or at least 25 years after the end of the study, whichever is longer." Added statement "It is the responsibility of the Sponsor to inform	To comply with necessary requirements for clinical studies conducted in EU Member States.

Section Number	Summary of Change	Rationale for Change
	the investigator as to when these documents no longer need to be retained."	
Section 12.2 Publication	Added paragraphs: "Irrespective of the outcome of the study, the Sponsor will submit a summary of the results of the clinical study to any relevant database within 1 year from the end of the global clinical study. It will be accompanied by a summary written in a manner that is understandable to laypersons. For studies conducted under Regulation EU 536/2014 where the study has ended in all Member States Concerned in the EU/European Economic Area (EEA) but is still ongoing in other regions and data from those regions are not available (making the statistical analysis not relevant), the summary of results must be submitted to the EU database as soon as it is available but no later than 1 year after the end of the study globally."	Added in language to document compliance with the legal requirement to report clinical study results. Added to represent necessary requirements for clinical studies conducted in EU Member States.
Appendix 17 EU GDPR- and CTR-Compliant Data Protection (New)	Added appendix regarding the measures that HUTCHMED Limited has put into place to meet the requirements of the Data Protection Laws for EU Member States.	Added detail regarding necessary requirements for clinical studies conducted in EU Member States.

EMERGENCY CONTACT

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
β-HCG	beta human chorionic gonadotropin
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	accumulation ratio
ARH-77	cell type derived from the peripheral blood of a patient with IgG plasma cell leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve in a selected time interval
AUC_{tau}	area under the drug concentration-time curve over the dose interval
$AUC_{tau,ss}$	area under the drug concentration-time curve over the dose interval at steady state
BCL-2	B-cell lymphoma-2
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BID	twice daily (or 2 times a day)
BLNK	B-cell linker protein
BOR	best overall response
B-NHL	B-cell non-Hodgkin's lymphoma
BTK	Bruton's tyrosine kinase
CBCL	cutaneous B-cell lymphoma
CCL	chemokine (C-C motif) ligand
CL	clearance
CL/F	apparent clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CR	complete response
CRi	complete response incomplete marrow recovery
CrCl	creatinine clearance (estimated per Cockcroft-Gault)
CRF	Case Report Form

Abbreviation	Definition
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEAS	efficacy evaluable analysis set
EU	European Union
EUA	Emergency Use Authorized
FAS	Full Analysis Set
FDA	Food and Drug Administration
FL	follicular lymphoma
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HL	Hodgkin's lymphoma
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	the concentration of a drug that is required for 50% inhibition in vitro
ICF	informed consent form
ICH	International Council for Harmonisation
IgM	immunoglobulin M
IHC	immunohistochemistry
INR	international normalized ratio
IRC	independent review committee
ITP	immune thrombocytopenia
IPI	International Prognostic Index
IRB/IEC	Institutional Review Board/Independent Ethics Committee

Abbreviation	Definition
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LPL	lymphoplasmacytic lymphoma
MATE	multidrug and toxin extrusion
MCL	mantle cell lymphoma
mDoR	median duration of response
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
MRP2	multidrug resistance protein
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
MZL	marginal zone lymphoma
NC	not calculable
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NOAEL	No-Observed-Adverse-Effect Level
nPR	nodular partial response
OATP	organic anion transporter protein
ORR	objective response rate
PCR	polymerase chain reaction
PD	progressive disease
PD1	programmed cell death protein 1
PFS	progression free survival
PKAS	pharmacokinetics analysis set
PI3K	phosphoinositide3'-kinase
PI3Kδ	phosphoinositide 3'-kinase δ
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PR	partial response
PR-L	partial response with lymphocytosis
PT	preferred term
PTCL	peripheral T-cell lymphoma
QD	once a day (from the Latin *quaque die*)
QTcF	corrected QT interval with Fridericia
REC-1	cell type derived from the mantle cell lymphoma
RES	response evaluable set
RNA	ribonucleic acid

Abbreviation	**Definition**
RP2D	recommended Phase II dose
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SLL	small lymphocytic lymphoma
SRC	Safety Review Committee
SYK or Syk	spleen tyrosine kinase
$t_{1/2}$	terminal half-life time
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma concentration
TTP	time to tumor progression
TTR	time to response
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady state
WM	Waldenström's macroglobulinemia

1 PROTOCOL SYNOPSIS

Protocol Number	2018-523-00US1
Title	A Phase I, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of HMPL-523 in Patients with Relapsed or Refractory Lymphoma
Study Phase	Phase I
Sponsor	HUTCHMED Limited
Study Drug	HMPL-523 CCI Tablets (from herein referred to as "HMPL-523")
Planned Enrollment	Approximately 131-155 patients were planned to be enrolled. As of Amendment 5, 48 patients have been enrolled, with 3 patients currently receiving treatment in the study.
Study Duration	Approximately 58 months Estimated duration for the entire study from screening period, through treatment period, and until the last subject completes treatment.
Study Status as of Protocol Amendment 5	The study is closed to new enrollment; the last patient was enrolled on CCI As of Amendment 5, 3 patients are receiving treatment in the study.
Study Objectives	Primary objectives: • To evaluate the safety and tolerability of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage • To determine the maximum tolerated dose (MTD)/recommended Phase II dose (RP2D) and characterize the dose-limiting toxicities (DLTs) associated with HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage • To evaluate the preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma in the dose expansion stage
	Secondary objectives: • To characterize the pharmacokinetics (PK) properties of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage and the dose expansion stage • To evaluate the safety and tolerability of HMPL-523 at the MTD/RP2D in patients with relapsed or refractory lymphoma in the dose expansion stage • To evaluate the preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage
	Exploratory objectives: • To evaluate the PK properties of CCI HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation and dose expansion stages • To explore biomarkers for progressive disease, predictive, and others (not exhaustive), including antitumor activities of HMPL-523
Study Design	This is a Phase I, open-label, multicenter study of HMPL-523 administered orally to patients with relapsed or refractory lymphoma who have exhausted approved therapy options as described in Section 4.1. This study consists of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2).

	Dose Escalation Stage (Stage 1) Dosing will begin at 100 mg orally, once daily (QD). A cycle of study treatment will be defined as 28 days of continuous dosing. The modified 3+3 design will be applied for dose escalation and MTD determination to limit the number of patients being exposed to potentially ineffective or unsafe doses. The study will enroll 1 patient, and the patient will be treated for a 28-day cycle in the initial dose cohort. If there is no DLT and no more than 2 treatment-emergent adverse events (TEAEs) of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 in the first treatment cycle, the study will be escalated to the next dose cohort and continue with the standard 3+3 design. Otherwise, the trial will revert to a standard 3+3 design from the initial dose cohort. A minimum of 3 patients will be enrolled in each cohort dose level and observed for toxicity in each successive dose cohort after the initial dose cohort. If the 3 patients initially enrolled in a given dose cohort complete the DLT assessment window (Cycle 1, Days 1-28, = C1D1-C1D28) without experiencing a DLT, 3 patients will be enrolled at the next higher dose level. If 2 or more of the initial 3 patients enrolled at any dose level experience a DLT during the DLT assessment window, the dose escalation will be halted. If 1 of the initial 3 patients enrolled at any dose level experiences a DLT during the DLT assessment window, additional patients will be enrolled at that dose level for a minimum of 6 evaluable patients for DLT. If a DLT is observed in 1 of the 6 evaluable patients at this dose level, dose escalation will proceed to the next pre-defined dose level. If DLTs are observed in 2 or more of the 6 evaluable patients at a given dose level, the dose escalation will be halted. If the dose escalation is completed due to 2 or more DLTs at a dose level and that dose level is ≥ 50% higher than the previous dose level, then an intermediate dose level may be evaluated for toxicity in the same manner as described above. If the dose level is < 50% higher than the previous dose level, in which only 3 DLT evaluable patients were enrolled, 3 additional patients will be enrolled at that dose level to comprise 6 DLT evaluable patients. The proposed dose escalation scheme comprises Cohorts 1 to 5 with oral dosing levels of 100 mg QD, 200 mg QD, 400 mg QD, 600 mg QD, and 800 mg QD, respectively. The need for dose escalation to a specific dose beyond 800 mg QD, or de-escalation to 700 mg QD will be evaluated jointly by the investigators and the sponsor based on the cumulative clinical safety, pharmacokinetic, and preliminary efficacy data. Safety monitoring and evaluation of dose escalation will be carried out by the Safety Review Committee (SRC), which will be comprised of the sponsor's study team members (including medical monitor, safety monitor and others as may be deemed necessary), and the sites' principal investigators. The SRC will determine whether it is safe to continue the assigned HMPL-523 dose for dose escalation or whether the dose should be de-escalated to the lower dose level. **Definition of Dose-Limiting Toxicity** DLT is defined as the occurrence of any of the following TEAEs during the DLT assessment window (C1D1-C1D28), unless clearly unrelated to the study drug: a. Nonhematologic toxicity: All nonhematologic TEAEs of Grade 3 or greater with the exception of: • Grade 3 nausea, vomiting controlled by supportive therapy b. Hematologic toxicity: • Grade 4 neutropenia lasting more than 5 days

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelets transfusion
- Grade 3 or greater febrile neutropenia (defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3℃ (101℉) or a sustained temperature of ≥ 38℃ (100.4℉) for more than one hour
- Grade 4 anemia unexplained 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, dose escalation, DLTs will be assessed during the DLT assessment window of 28 days (ie, from Cycle 1 Day 1 [the day of first administration of treatment] through to Cycle 1 Day 28).

Definition of DLT Evaluable Patient

For decisions on dose escalation, each dose cohort shall present protocol-required number of DLT-evaluable patients. A patient 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

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

Dosing Beyond Cycle 1

Patients who complete the DLT assessment window (Cycle 1 Days 1-28) and are deemed by the investigator to be benefiting from HMPL-523 treatment may continue with HMPL-523 treatment until disease progression, intolerable toxicity, at the investigator's discretion that the patient can no longer benefit from the study treatment, patient withdrawal from the study, the end of study, or death, whichever comes first.

Definition of MTD

The MTD is defined as the maximum dose at which no more than 16.7% of patients in a single cohort experiences a DLT in the first cycle (Cycle 1 Days 1-28).

Definition of RP2D

The decision regarding the RP2D took the following into consideration:

- Maximum tolerated dose if reached
- Pharmacokinetics with or without associated safety and preliminary efficacy findings

These criteria constituted the basis for RP2D determination. Both the sponsor and the investigators agreed upon the RP2D.

Based on evaluation of data collected during the dose escalation phase, the RP2D has been determined to be 700 mg once daily.

	Dose Expansion Stage (Stage 2) The safety, tolerability, PK, and preliminary efficacy of HMPL-523 at MTD/RP2D, which has been determined to be 700 mg once daily, will be further evaluated in patients with relapsed or refractory non-Hodgkin's and Hodgkin's lymphomas. **Amendment 5** As of CCI no new patients were enrolled in the study. The study is now closed to enrollment. A total of 48 patients were enrolled in the dose-expansion portion at the time of enrollment closure. At the time of Amendment 5, approximately 3 patients are continuing study treatment. **Safety Monitoring** In addition to periodic safety review by the SRC for dose escalation decisions, routine safety monitoring for all enrolled patients will be carried out by the investigators and the sponsor after informed consent has been obtained until 30 days following the last treatment dose or study discontinuation/termination, whichever is later. After this period, investigators should report only serious adverse events (SAEs) that are related to prior HMPL-523 treatment. All adverse events (AEs) will be graded in accordance with the National Cancer Institute (NCI) CTCAE version 5.0. **Tumor Assessment** Tumor response will be assessed by investigators according to the response criteria for the respective diseases every 8 weeks (±7 days), for the first 24 weeks, and every 12 weeks (±7 days) thereafter. Tumor assessment will also be conducted at study completion or at early termination visit (for reasons other than disease progression). **Follow-up (Extended Monitoring)** Patients who discontinue the study drug due to reasons other than disease progression will remain on the study and will be followed quarterly for tumor assessment until the patient has the first progression, starts new anticancer therapy, or dies or until 12 months after the initial dose of the study drug, whichever comes first. **End of Study** The end of the study is defined as the date on which all patients have their last visit or 2 years after the last patient has his/her first visit, whichever comes first.
Study Treatment	HMPL-523 is in tablet formulation, orally administered daily by patients.
Inclusion Criteria	Patients must meet the following criteria to be eligible for study entry: 1. Signed informed consent form 2. Age ≥ 18 years 3. Eastern Cooperative Oncology Group performance status of 0 or 1 4. Histologically confirmed lymphoma, including Hodgkin's lymphoma and non-Hodgkin's lymphoma. In the dose expansion stage, the tumor types may be restricted to any or all of the following tumor types. There may be approximately 10 patients in each cohort depending on response signals suggesting efficacy, except for HL cohort with 25 patients and 2 identified cohorts with approximately 20 patients per cohort: relapsed or refractory chronic lymphocytic leukemia

	(CLL)/ small lymphocytic lymphoma (SLL) (n = 10), and CLL/SLL post-Bruton's tyrosine kinase (BTK) exposure (n = 20), mantel cell lymphoma (MCL), follicular lymphoma (FL) (Grade 1-3a) (n = 20), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL), peripheral T-cell lymphoma (PTCL), and cutaneous B-cell lymphoma (CBCL). As of Amendment 5, the study is closed to new enrollment. 5. Patients with relapsed or refractory lymphoma who have exhausted all approved therapy options as defined below: a. 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 b. Those who can no longer tolerate/withstand cytotoxic chemotherapy and/or available standard of treatment/care. Where safety profile and risks of toxicity of other treatment options far outweigh any possible clinical benefit c. Those with no curative standard of treatment or where available treatments are not reasonable or do not make sense. In particular, those who, in the opinion of the attending principal investigator, will benefit from a new class of compound with a different mechanism of action d. Patients enrolled in the post-BTK CLL cohort should have either disease progression or intolerance to prior BTK inhibitor therapy to enroll. Approximately 10 out of the 20 patients in this cohort should also have either disease progression or intolerance to prior B-cell lymphoma-2 (BCL-2) (venetoclax or BCL-2 inhibitor on clinical trial) exposure. 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, HL, or SLL defined as at least 1 bi-dimensionally measurable lesion (nodal disease > 1.5 cm, non-nodal disease > 1 cm in its longest dimension by computed tomography scan) 7. Availability of tumor sample for patients in dose expansion cohorts: This may be an archival tissue sample obtained after most recent therapy or a fresh biopsy; if tumor sample is not available, the sponsor may waive the requirement after discussion 8. Expected survival of more than 24 weeks as determined by the investigator 9. Patients with prior treatment with any spleen tyrosine kinase (SYK) inhibitors (eg, fostamatinib) are eligible for escalation stage 1. However, during expansion stage 2, only patients who discontinue SYK inhibitors for reasons other than disease progression are eligible 10. Male patients must agree to use a condom and female patients of child-bearing potential must agree to use highly effective contraceptive measures for 30 days after the last dose of study drug. These highly effective contraceptive measures, as defined by the Clinical Trials Facilitation Group, include as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine contraceptive device, intrauterine hormone release system, bilateral tubal occlusion, or a vasectomized partner, provided that male partner is the sole sexual partner of the female patient. Postmenopausal females (women who have not had menses for at least 1 year without an alternative medical cause) are exempt from this criterion.
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from study entry:

	1. Patients with primary central nervous system lymphoma 2. Any of the following laboratory abnormalities: a. Absolute neutrophil count < 1.0×10^9/L b. Hemoglobin < 80 g/L c. Platelets < 50×10^9/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 believed to be splenic involvement or bone marrow infiltration. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval (confirmed in writing) by the sponsor will a patient with cell counts below the thresholds be enrolled in the study. In the dose expansion stage, patients with Grade ≤ 2 neutropenia per CTCAE v5.0 and/or thrombocytopenia and with confirmed splenic involvement or bone marrow infiltration are eligible. 3. Inadequate organ function, defined by the following: a. Total bilirubin > 1.5 times the upper limit of normal (× ULN) with the following exception: • Patients with known Gilbert's disease who have serum bilirubin level ≤ 3 × ULN and normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may be enrolled. b. AST and/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. c. Estimated creatinine clearance (CrCl) per Cockcroft-Gault • Dose escalation portion of trial (Stage 1) CrCl < 40 mL/min • Dose expansion portion of trial (Stage 2) CrCl < 30 mL/min d. Serum amylase or lipase > ULN e. International normalized ratio >1.5 × ULN or activated partial thromboplastin time > 1.5 × ULN **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 (confirmed in writing) by the sponsor will a patient with impaired kidney function due to underlying disease be enrolled in the study. 4. Patients with clinically detectable second primary malignant tumors at enrollment or other malignant tumors within the last 2 years (with the exception of radically treated basal cell or squamous cell carcinoma of the skin, in situ cervix, or in situ breast cancer) 5. Any anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, vaccine, or radiotherapy, within 3 weeks prior to initiation of study treatment 6. Herbal therapy within 1 week prior to the initiation of study treatment (3 weeks for St. John's wort) 7. Prior administration of radioimmunotherapy within 3 months before the initiation of study treatment 8. Use of strong cytochrome P450 enzyme (CYP)3A4 inhibitors or inducers and substrates of CYP3A4, CYP2B6, or CYP1A2, which are identified as narrow therapeutic drugs, within 14 days prior to the initiation of study treatment

	9. Adverse events from prior anticancer therapy that have not resolved to Grade ≤1, except for alopecia 10. Prior autologous stem cell transplant within 6 months prior to the initiation of study treatment 11. Prior allogeneic stem cell transplant within 6 months prior to the initiation of study treatment or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to the initiation of study treatment 12. Clinically significant active infection (eg, pneumonia) and interstitial lung diseases 13. Major surgical procedure within 4 weeks prior to the initiation of study treatment 14. Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with human immunodeficiency virus, hepatitis B virus (HBV), hepatitis C virus (HCV), or cytomegalovirus (CMV) – Active infection is defined as one requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody [HBcAb]) or HCV antibody. – Patients who are positive for HBcAb are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction is negative for HBV deoxyribonucleic acid. – Patients who are positive for HCV serology are only eligible if test result for HCV ribonucleic acid is negative. – CMV antibody will be tested at screening, and if positive, viral load will be determined. Patients who are positive for CMV antibody are only eligible if the test result for CMV DNA is negative. 15. Pregnant (positive serum beta human chorionic gonadotropin [β-HCG] or urine test) or lactating women 16. New York Heart Association Class II or greater congestive heart failure 17. Congenital long QT syndrome or corrected QT interval with Fridericia > 480 msec 18. Current use of medication known to cause QT prolongation or Torsades de Pointes 19. History of myocardial infarction or unstable angina within 6 months prior to the initiation of the study treatment 20. History of stroke or transient ischemic attack within 6 months prior to the initiation of the study treatment 21. Inability to take oral medication, prior surgical procedures affecting absorption, or active peptic ulcer disease 22. Treatment in a clinical study within 30 days prior to the initiation of study treatment 23. Ongoing psychiatric disorder, in particular, patients with depression and/or suicidal tendencies 24. Patients with pathological or organic fractures, in particular, those of unknown etiology 25. 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, may affect the interpretation of the results, or renders the patient at high risk from treatment complications

Outcome Measures	
Safety Assessment Parameter	Primary safety outcome measure: • Incidence of DLTs by NCI CTCAE v5.0 grade and associated dose of HMPL-523 Secondary safety outcome measures: • Incidence of TEAEs by NCI CTCAE v5.0 grade and associated dose of HMPL-523 • Incidence of Grade 3 and 4 abnormalities in safety related-laboratory parameters and associated dose of HMPL-523 • Incidence of TEAEs leading to HMPL-523 dose interruption, reduction, or treatment discontinuation
Pharmacokinetic Assessment Parameter	Pharmacokinetic outcome measures: • Maximum plasma concentration • Time to reach maximum plasma concentration • Area under the concentration-time curve in a selected time interval • Area under the concentration-time curve during one dosing interval • Apparent clearance • Minimum plasma concentration • CCI drug ratio • Accumulation ratio
Efficacy Assessment Parameter	Efficacy outcome measures: • Objective response rate (ORR) is defined as the proportion of patients who have a best overall response (BOR) of CR or PR. The BOR in an individual patient is the best response recorded from the start of treatment until progression or the date of any further anticancer therapy, whichever comes first. • Duration of response (DoR) is defined as the time from when the first response (CR or PR) was achieved until the first documentation of definitive disease progression or death from any cause, whichever occurs first. • Time to response (TTR) is defined as the time from the date of the first dose of the study drug to first response (CR or PR). • Progression free survival (PFS) is defined as time from the date of the first dose of the study drug until the date of disease progression or death due to any cause. Efficacy in different subgroups will be evaluated according to specified guidelines/criteria: • Chronic lymphocytic leukemia: the modified International Workshop on CLL guideline (modified International Workshop on Chronic Lymphocytic Leukemia [IWCLL] 2008) • WM/LPL: consensus of international workshops on WM (IWWM-7 Consensus) • Lymphomas other than CLL or WM/LPL: Lugano Response Criteria for Hodgkin and Non-Hodgkin's Lymphoma.
Statistical Methods	**Determination of Sample Size** The study is closed to new enrollment; the last patient was enrolled on CCI The total number of patients enrolled in the dose-expansion

	phase of the study at the time of enrollment closure is 48, with 3 patients continuing on treatment. The sample size rationale for the study prior to closing for further enrollment is described below. **Stage 1: Dose Escalation** The sample size for Stage 1 is based on the dose-escalation rules of the 3 + 3 design. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 such AE in a given cohort of 6 patients is 46.9%, 26.5%, and 5.8%, respectively. **Stage 2: Dose Expansion** The planned enrollment for Stage 2 was approximately 70 patients. A total of 70 patients will provide more robust safety data in the patient populations studied. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 such AE in 70 patients is 99.9%, 97.2%, and 50.5%, respectively.
Safety Analysis	Data will be summarized by dose level, subtype of malignancy, and overall, as appropriate. The DLTs will be listed. The incidence of TEAEs, SAEs, AEs of special interest, and AEs leading to dose interruption, reduction, or treatment discontinuation will be presented by Medical Dictionary for Regulatory Activities System Organ Class and preferred term, by relationship to study drug, by toxicity grade, and by severity for each dose level, and by type of malignancy. For laboratory tests that are graded by NCI CTCAE v5.0 or higher, results will be summarized by grade. Descriptive statistics for vital signs and 12-lead electrocardiogram parameters will be presented by dose level and visit and also by type of malignancy and visit. Physical examinations findings will be listed.
Pharmacokinetic Analysis	A noncompartmental model analysis will be performed for plasma concentration data by a central laboratory using Phoenix WinNonlin. Individual and mean plasma concentration of HMPL-523 and CCI versus time data will be tabulated and presented. Descriptive statistics (n, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation) for all of the relevant PK parameters of HMPL-523 and CCI will be presented.
Efficacy Analysis	Data will be summarized by dose level, subtype of malignancy (when feasible), and overall, as appropriate. The estimated ORR and 95% confidence interval will be presented for each type of malignancy. Where data allows, median PFS, TTR, and DoR will be estimated, and the Kaplan-Meier curve will be plotted for each type of malignancy.

2 BACKGROUND

Lymphoma is the most common hematologic malignancy caused by neoplastic proliferation of the normal lymphocyte and is divided into 2 types: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). B-cell NHL (B-NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes and range from slow-growing indolent and incurable diseases (eg, follicular lymphoma [FL] or chronic lymphocytic leukemia [CLL]) with a median survival of 810 years to more aggressive lymphomas (eg, diffuse large B-cell lymphoma [DLBCL]) with a median survival of 6 months if left untreated or long-term remission in more than 50% of patients with appropriate treatment. Mantle cell lymphoma (MCL) shares characteristics of both types, being incurable with a short remission. DLBCL is the most common type of NHL and accounts for approximately 30---40% of all new cases, whereas FL and MCL account for approximately 20-25% and 6-10% of all new cases, respectively, of other lymphomas.

B-cell CLL is the most common chronic leukemia in adults in Western countries and has been classified as a mature B-cell malignancy according to the 2016 revision of the World Health Organization classification of lymphoid neoplasms (Swerdlow et al 2017). Waldenström's macroglobulinemia (WM, also known as lymphoplasmacytic lymphoma [LPL]) 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 (IgM), thickening the blood, and infiltrate the bone marrow with lymphoplasmacytic cells. Currently, median survival is 6.5 years. First-line therapy should consist of the monoclonal anti-CD20 antibody. Relapse is almost inevitable and may occur years after initial therapy.

In 2017, there were an estimated 72240 new incident cases of NHL and 8260 new incident cases of HL in the United States (US). These 2 types of malignancy resulted in approximately 20140 and 1070 deaths, respectively. NHL ranked 7th for cancer incidence and 8th for cancer death in the US. The estimated 5-year overall survival of patients with NHL or HL was 71.0% and 86.4%, respectively (National Cancer Institute 2018). NHL alone caused 6.3 million disability-adjusted life years in 2015 (Global Burden of Disease Cancer Collaboration et al 2017).

2.1 Current Therapies and Unmet Medical Need

Despite improvements in clinical outcomes of patients with NHL due to advances in treatments (including the CD20-specific monoclonal antibody rituximab; ofatumumab and obinutuzumab; idelalisib and ibrutinib, which target the B-cell receptor [BCR] pathway; lenalidomide; the B-cell lymphoma-2 (BCL-2) inhibitor venetoclax; and inhibitors of programmed cell death protein 1 [PD1] or PD1 ligand 1 [PDL1]), some indolent B-cell malignancies remain incurable, as do approximately half of the aggressive NHLs.

The BCR signaling pathway plays a crucial role in the survival, proliferation, and trafficking of NHL cells. Inhibitors of the key kinases in this pathway, including phosphoinositide 3'-kinase (PI3K), Bruton's tyrosine kinase (BTK), and spleen tyrosine kinase (SYK) have been found to decrease NHL cell viability in nonclinical models and clinical studies. In fact, several PI3K inhibitors (idelalisib, copanlisib) and BTK inhibitors (ibrutinib, acalabrutinib) have been approved recently by the Food and Drug Administration (FDA) for the treatment of CLL/small

lymphocytic lymphoma (SLL), FL, marginal zone lymphoma (MZL), MCL, and WM. However, not all NHLs will respond to newly approved PI3K or BTK inhibitors.

Another pathway that has been a successful strategy for targeted therapy in CLL is the overexpression of BCL-2, which confers resistance to apoptosis. Venetoclax, an oral inhibitor of BCL-2, induces apoptosis in CLL cells and has been shown to be another effective chemotherapy-free strategy in both relapsed/refractory and treatment-naïve CLL patients (Wierda and Tambaro 2020). Venetoclax is FDA approved for use in both upfront and relapsed/refractory CLL. Many, if not most, CLL patients are managed with BTK inhibitors and venetoclax as their first two lines of therapy. An emerging unmet need in the clinic is the management of patients who have developed resistance to both targeted therapies, so called "double refractory" patients (Aronson et al 2022).

Syk expression by immunohistochemistry in patients with HL was found to be significantly associated with shorter failure-free survival (Martin et al 2011). Targeting Syk may be a novel strategy for the treatment of HL.

Therefore, more effective and safer therapies are required for patients with relapsed or refractory lymphoma, especially for patients that have progressed or are intolerant to BCR inhibitors.

2.2 Background on HMPL-523

2.2.1 Nonclinical Pharmacology

HMPL-523 is a selective small-molecule SYK inhibitor. HMPL-523 has shown good selectivity in a kinase selectivity panel and a broad pharmacological panel of 79 targets including receptors and ion channels. At the molecular level, HMPL-523 inhibited SYK kinase with the concentration of a drug that is required for 50% inhibition in vitro (IC_{50}) of CCI μM. At the cellular level, HMPL-523 effectively inhibited SYK activity and activation of B-cell linker protein (BLNK), a downstream signal molecule of SYK, in the cell type derived from the mantle cell lymphoma (REC-1) MCL cell line and the cell type derived from the peripheral blood of a patient with IgG plasma cell leukemia (ARH-77) human plasma cell leukemia cell line with an IC_{50} of CCI μM and CCI μM, respectively. By inhibiting activation of the SYK signaling pathway, HMPL-523 significantly inhibited REC-1 and ARH-77 cell survival and induced apoptosis of REC-1. HMPL-523 inhibited the survival of multiple B-NHL cell lines. In primary B-cells obtained from 2 patients with CLL, HMPL-523 potently inhibited anti-IgM-stimulated survival and significantly inhibited the production of chemokine ligands chemokine (C-C motif) ligand CCL3 and CCL4, which are important for cancer cell homing, implying these 2 cytokines may be candidates for predictive biomarkers for instance. Knowledge of this may be valuable for patient stratification purposes.

HMPL-523 also exerted a significant antitumor effect in B-NHL malignant xenograft models by CCI oral dosing. HMPL-523 inhibited tumor growth in a subcutaneous xenograft of MCL REC-1 with tumor growth inhibition of CC % at the dose of C mg/kg. In a $Ba/F3^{TEL\text{-}SYK}$ bearing mice model, HMPL-523 inhibited phosphorylation of SYK and its downstream signaling pathway and prolonged the lifespans of $Ba/F3^{TEL\text{-}SYK}$ bearing mice with increases in lifespan of CCI, and CCI % at the dose of CCI, and C mg/kg, respectively, in a dose-dependent manner.

HMPL-523 was also evaluated in an acute myeloid leukemia (AML) cell line with aberrant Flt3 activation. HMPL-523 inhibited proliferation of the MV-4-11 AML cell line (Flt3-ITD+) with an IC_{50} of CCI μM. In line with its Flt3 kinase and cellular activity in vitro, HMPL-523 showed potent antitumor efficacy in the MV-4-11 tumor model with tumor growth inhibitions of CCI, CCI and CC % at CCI mg/kg, respectively.

Results of safety pharmacology studies showed that HMPL-523 had a low risk on the cardiovascular, central nervous, and respiratory systems.

2.2.2 Nonclinical Pharmacokinetics

The pharmacokinetic (PK) properties and metabolic profile of HMPL-523 were evaluated both in vitro and in vivo in different nonclinical species. HMPL-523 was found to have moderate to high intrinsic membrane permeability and good oral absorption in mice, rats, and dogs. HMPL-523 showed low clearance (CL) and moderate volume of distribution at steady state (V_{ss}) in mice and rats but high CL and V_{ss} in CCI dogs, and monkeys. In rats, HMPL-523 was extensively distributed into organs with abundant blood perfusion such as lung, spleen, liver, kidney, and pancreas as well as some gastrointestinal organs such as colon and stomach. HMPL-523 crossed the blood-brain barrier with difficulty, as indicated by CCI lower concentrations in the brain and spinal cord than in the plasma.

A total of 8 metabolites were identified after HMPL-523 was incubated with liver microsomes and S9 fractions from different species. After oral administration in rats, HMPL-523 was extensively metabolized into CCI M3 was the predominant metabolite in both in vitro and in vivo circulatory systems in rats and dogs. CCI The metabolic profiles in rats and dogs appeared to cover all types of metabolites formed in in vitro metabolism assays using human liver microsomes and S9 fractions CCI. Fecal excretion was the major excretion route of [^{14}C]HMPL-523 after oral administration, with an excretion rate of approximately 90% of the dose, in which 20% of radioactivity was recovered in bile. Only a small amount of radioactivity was excreted via kidney. HMPL-523 was a P-glycoprotein (P-gp) substrate but not a substrate of breast cancer resistance protein (BCRP), organic anion transporter protein (OATP)1B1, and OATP1B3. HMPL-523 or its CCI CCI showed limited inhibitory effects on most cytochrome P450 enzyme (CYP) 450 isoforms in either a reversible or time-dependent manner. HMPL-523 was a possible weak inducer of CYP3A, 1A2, and 2B6 based on in vitro data. Although HMPL-523 and C showed in vitro inhibitory effects on P-gp, BCRP, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), OATP1B1, OATP1B3, OCT2, MRP2, multidrug and toxin extrusion protein (MATE) 1, and MATE2-K, clinical drug-drug interactions (DDI) is only expected with P-gp, BCRP, MATE1, and MATE2-K substrates when human exposure was taken into account.

2.2.3 Nonclinical Toxicology

The safety profile of HMPL-523 was evaluated in multiple studies under Good Laboratory Practice (GLP) guidelines. In summary, the maximum tolerated dose (MTD) was C mg/kg in single dose toxicity studies with rats and dogs. In GLP repeat-dose toxicity studies in rats and dogs, the main toxicity target organs included the CCI,

CCI in both species, and CCI (rats only). In addition, CCI and CCI were increased in both rats and dogs with CCI in rats, but without any observations in dogs. The histopathology findings of CCI in rats might be species specific. The major findings in repeat-dose toxicity studies were reversible after withdrawal of the drug. In the 9-month toxicity study in dogs, presence of CCI in CCI CCI were noted at the end of the dosing and recovery phases. This finding can be observed in CCI However, the relationship to HMPL-523 was uncertain.

HMPL-523 was not genotoxic based on the battery of *in vitro* and *in vivo* genotoxicity studies.

In the rat fertility and early embryo-fetal development study, CCI were noted CCI, but no effects were observed on female fertility and early embryo-fetal development up to C mg/kg/day, the highest dose evaluated. The No-Observed-Adverse-Effect Level (NOAEL) for female fertility and early embryo-fetal development was C mg/kg/day. At a dose of C mg/kg/day, changes in CCI CCI were found in male rats; as a result, the NOAEL for male fertility was C mg/kg/day. In the embryo-fetal development toxicity study in rats, at the dose of C mg/kg/day, CCI on the fetus was noted as well as maternal CCI As a result, the NOAEL for maternal and embryo-fetal developmental toxicity in rats was C mg/kg/day. In the embryo-fetal development toxicity study in rabbits, a dose of C mg/kg/day was CCI by the dams, but no effect on embryo fetal development was noted. The NOAEL for maternal toxicity was C mg/kg/day, and the NOAEL for embryo/fetal development was C mg/kg/day.

HMPL-523 was not phototoxic based on the results of the in vivo phototoxicity study in Sprague Dawley rats with single doses up to C mg/kg, the highest dose employed. HMPL-523 and the CCI were also evaluated in the in vitro neutral red uptake assay with BALB/c 3T3 mouse fibroblast cells. Both HMPL-523 CCI were not phototoxic in this in vitro assay. Thus, HMPL-523 is considered not to present a phototoxic hazard to patients.

CCI, and its toxicity was evaluated in a 13-week repeat-dose toxicity study in rats by the subcutaneous route with doses up to mg/kg/day. CCI CCI. Based on the totality of the results of a standard battery of genotoxicity evaluations, CCI (negative results in bacterial mutation tests and *in vivo* micronucleus and liver comet assays despite being positive in in vitro chromosome aberration tests). In the embryo-fetal developmental toxicity study in rats, CCI changes included CCI at the high dose of C mg/kg/day. No effects on reproductive function and embryo-fetal development toxicity were observed at all doses. The NOAEL was mg/kg/day for parental pregnant rats; the NOAEL was C mg/kg/day for reproductive function and embryo-fetal development.

More detailed safety evaluation results with HMPL-523 CCI in genotoxicity, safety pharmacology, fertility and early embryonic developmental toxicity, and embryo-fetal developmental toxicity are provided in the investigator's brochure (IB).

2.2.4 Clinical Experience

As of 10 May 2022, 7 clinical studies of HMPL-523 were developed by HUTCHMED Limited (4 completed, 3 ongoing). Completed studies are 1 Phase I mono-therapy study in healthy volunteers (Study 2014-523-00AU1, conducted in Australia, https://clinicaltrials.gov/ct2/show/NCT02105129), 1 Phase I mono-therapy study in patients with relapsed or refractory mature B-cell neoplasms (Study 2015-523-00CH1, conducted in China, https://clinicaltrials.gov/ct2/show/NCT02857998), 1 Phase Ib double-blind study in patients with primary immune thrombocytopenia (ITP) (Study 2018-523-00CH1, conducted in China, https://clinicaltrials.gov/ct2/show/NCT03951623), and 1 Phase I combo-therapy study in patients with AML (Study 2017-523-00CH3, conducted in China, https://clinicaltrials.gov/ct2/show/NCT03483948). Ongoing studies are 2 Phase I mono-therapy studies in patients with hematologic malignancies (Study 2015-523-00AU1, conducted in Australia, https://clinicaltrials.gov/ct2/show/NCT02503033; and 2018-523-00US1, study described in this protocol, conducted in the US and the European Union [EU], https://clinicaltrials.gov/ct2/show/NCT03779113), and 1 Phase III double-blind study in patients with primary ITP (Study 2020-523-00CH1, conducted in China, https://clinicaltrials.gov/ct2/show/NCT05029635).

Summary results for ongoing studies below are as of 10 May 2022.

Refer to the IB for further information.

2.2.4.1 Study 2014-523-00AU1 in Healthy Volunteers

This design of this completed study included 3 parts. **Part A** was a randomized, double-blind, placebo-controlled, single ascending dose stage, in which HMPL-523 5 mg, 20 mg, 50 mg, 100 mg, 200 mg, and 300 mg were administered under fasted conditions, followed by HMPL-523 300 mg, 400 mg, 600 mg, and 800 mg under fed conditions with a standard meal. **Part B** was a randomized, double-blind, placebo-controlled, multiple ascending dose stage, in which HMPL-523 200 mg, 300 mg, and 400 mg was administered QD for 14 days with a standard meal. **Part C** was an open-label, single dose, cross-over study designed to investigate the effect of food on the PK of HMPL-523, in which subjects received a single dose of HMPL-523 100 mg under fasted conditions (Period 1) followed by a 7-day washout period and then a single dose of HMPL-523 100 mg with a high-fat meal (Period 2).

Safety

Part A

A total of 80 subjects (10 cohorts of 8 subjects) were enrolled in Part A, 60 subjects were dosed with HMPL-523, and 20 subjects were dosed with placebo. All subjects completed the study as planned.

Fifteen treatment-emergent adverse events (TEAEs) were reported during the study period by 12 subjects (20.0%) who received HMPL-523, and 3 TEAEs were reported by 3 subjects (15.0%) who received placebo. No dose-limiting toxicities (DLTs) and serious adverse events (SAEs) were observed. No TEAEs were considered probably or definitely related to HMPL-523 and 9 TEAEs were considered possibly related to HMPL-523 by the investigators. TEAEs occurring in more than 1 subject included headache (n = 5), upper respiratory tract infections (n = 3), and back pain (n = 2).

Part B

A total of 32 subjects (4 cohorts of 8 subjects) were enrolled in Part B and dosed with HMPL-523 (n = 24) or placebo (n = 8). Four subjects did not complete the study as planned due to TEAEs, which included 1 elevated lipase and 1 seborrheic dermatitis in the 200-mg dose cohort, and 1 pyrexia and 1 malaise in the 400-mg dose cohort.

A total of 51 TEAEs were reported during the study by 19 subjects (79.2%) who received HMPL-523, and 10 TEAEs were reported by 6 subjects (75.0%) who received placebo. Two DLTs were observed and reported as SAEs. These were 1 elevated lipase (200-mg cohort) and 1 pyrexia (400-mg cohort). The majority of TEAEs reported in the HMPL-523 treatment groups were mild in intensity. A total of 12 events reported by 8 subjects were moderate in intensity, and SAEs that were determined to be DLTs were considered severe in intensity. Three TEAEs (elevated lipase, pyrexia, and elevated alanine aminotransferase [ALT]) reported by 3 subjects were considered probably related to HMPL-523; 29 TEAEs reported by 15 subjects were considered possibly related to HMPL-523. TEAEs reported by more than 1 subject who received HMPL-523 included headaches (n = 11), increased ALT (n = 5), dizziness (n = 3), malaise (n = 3), upper respiratory tract infections (n = 3), increased lipase (n = 2), somnolence (n = 2), lethargy (n = 2), constipation (n = 2), and back pain (n = 2).

Part C

A total of 6 subjects (1 cohort) were enrolled in Part C and received a single dose of HMPL-523 100 mg under fasted conditions (Period 1). Following a washout period of 7 days, each subject received a single dose of HMPL-523 100 mg with a high-fat meal (Period 2). All subjects completed the study as planned.

A total of 4 subjects (66.7%) reported TEAEs after receiving a single dose of HMPL-523 under fasted conditions. No DLTs or SAEs were observed. TEAEs reported by at least one subject include pain in extremity (n = 2), plantar fasciitis (n = 1), and cough (n = 1). Three TEAEs (2 pains in extremity and 1 plantar fasciitis) were mild in intensity, and 1 TEAE (cough) was moderate in intensity. All TEAEs were considered to be not related to HMPL-523.

Pharmacokinetics

Exposures to HMPL-523 as measured by maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) after administration of single doses of 300 to 800 mg to fed subjects were approximately dose-proportional, as were exposures after administration of multiple doses of 200 to 400 mg, with low to moderate variability. Administration with a high-fat meal increased HMPL-523 C_{max} and AUC by approximately 1.6- and 1.5-fold, respectively, compared with administration of HMPL-523 after an overnight fast. The binding of HMPL-523 to human plasma protein in vitro was 82.9% and was not concentration-dependent in the range of 0.5 to 5 µM. The apparent oral clearance ranged from 236 to 376 L/h, and the apparent body volume ranged from 3340 to 6480 L, respectively, across all single dose levels from 100 to 800 mg.

Metabolism is the main route of elimination for HMPL-523. [redacted] The elimination half-life ranged between 9.8 hours and 13.5 hours across HMPL-523 doses of 100 to 800 mg and was not prolonged at steady state after multiple doses.

Pharmacodynamics

The inhibitory potency of HMPL-523 on anti-IgE-induced basophil activation (CD63+ expression) was evaluated in Part B. [redacted]

2.2.4.2 Study 2017-523-00CH3 Phase I Study in Patients with AML

This study was completed on 16 March 2020. Overall, 7 patients were enrolled including 3 patients in 400 mg QD cohort and 4 patients in 600 mg QD cohort. The patients received 400 mg QD or 600 mg QD of HMPL-523 in 28-day cycles together with subcutaneous injection of 75 mg/m^2 azacitidine on Day 1 to Day 7 of each cycle.

Safety

Based on the full analysis set (N = 7) in this study, all patients reported at least one TEAE, HMPL-523-related TEAE, and azacitidine-related TEAE.

Six (85.7%) patients reported HMPL-523-related TEAE of Grade ≥ 3, which included (≥ 30% of patients reported) platelet count decreased (71.4%), white blood cell count decreased (57.1%), neutrophil count decreased (42.9%), and pneumonia (42.9%).

Six (85.7%) patients reported azacitidine-related TEAE of Grade ≥ 3, which included (≥ 30% of patients reported) platelet count decreased (71.4%), white blood cell count decreased (57.1%), neutrophil count decreased (42.9%), and pneumonia (42.9%).

One patient (03001, 600 mg QD) experienced a DLT event, aspartate aminotransferase (AST) increased (Grade 3).

Four SAEs were reported in 4 patients (57.1%) out of a total of 7 patients who received the combo-treatment.

Pharmacokinetics

According to the data, when co-administered with azacitidine, the PK profile of HMPL-523 was not affected significantly with similar exposures on Day 7 and Day 28 (400 mg QD: geomean AUC_{tau}: 2250 h·ng/mL on Day 7 and 2940 h·ng/mL on Day 28; 600 mg QD: geomean AUC_{tau}: 4090 h·ng/mL on Day 7 and 4410 h·ng/mL on Day 28). For azacitidine, the geomean AUC_{tau} was 1480 and 1120 h·ng/mL on Day 7, respectively, when co-administered with 400 mg and 600 mg QD of HMPL-523.

Efficacy

Based on the efficacy evaluable set (N = 6), one patient had best of response (BOR) as complete response (CR) with incomplete hematologic recovery (CRi); one had partial response (PR). All tumor assessments from the other 4 patients were evaluated as stable disease (SD).

2.2.4.3 Study 2015-523-00AU1 Phase I Study in Patients with Relapsed or Refractory Hematologic Malignancies

This is an ongoing Phase I, open-label, study of the safety and PK of HMPL-523 in patients with relapsed or refractory hematologic malignancies in Australia. This study includes 2 stages: a

dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). In the dose escalation stage, the conventional 3+3 design was applied for dose escalation and determination of the MTD. A total of approximately 18 to 27 DLT evaluable patients will be enrolled into the QD or the twice a day (BID) regimen cohort in the dose escalation stage. The starting dose of HMPL-523 was 100 mg QD or 300 mg BID, respectively, administered orally in continuous 28-day cycles. In the dose expansion stage, approximately 40 patients with relapsed or refractory B-cell NHL or CLL will be enrolled at the recommended Phase 2 dose (RP2D) to further evaluate the safety, PK, and efficacy of HMPL-523.

Safety

CCI [redacted]

Pharmacokinetics

The preliminary PK data of HMPL-523 on Day 1, Day 15, and Day 28 for multiple 100 to 1000 mg QD and 300 mg and 400 mg BID doses in the dose escalation stage, and on Day 1 and Day 28 for the 600 mg and 800 mg QD cohorts in the dose expansion stage were available. In this study, all patients were instructed to take HMPL-523 at approximately 30 minutes after a meal.

Median time to reach maximum plasma concentration (T_{max}) values for HMPL-523 ranged from 2.00 to 6.05 hours following multiple 100 to 1000 mg QD doses, and from 1.89 to 4.08 hours following multiple 300 mg and 400 mg BID doses. The oral apparent clearance (CL/F) at steady state ranged from 164 to 369 L/h. The mean accumulation ratio (AR) for AUC_{tau} ranged from 1.31 to 2.13 following multiple QD doses, and from 1.93 to 3.70 following multiple BID doses. In general, lower C_{max}, higher minimum plasma concentration (C_{min}) and higher AR for AUC_{tau} were observed with BID dosing compared to QD dosing at the same total daily dose.

Systemic exposures of HMPL-523 increased with dose up to 1000 mg QD on Day 1 and up to 800 mg QD on Day 15 and Day 28. The exposures at steady state appeared to drop off when dose increased from 800 mg QD to 1000 mg QD. The reason is unclear but may be related to the large between-subject PK variability (around 60% to 80%) in comparison to the small dose increment (25% increase in dose from 800 to 1000 mg). In the dose escalation stage, the highest geometric mean exposure was achieved following the 800 mg QD dose on Day 15 with AUC_{tau} of approximately 4890 h·ng/mL and C_{max} of approximately 385 ng/mL. In the dose expansion stage, the geometric mean AUC_{tau} and C_{max} on Day 28 were 3330 h·ng/mL and 246 ng/mL, respectively, at 800 mg QD, and 2710 h·ng/mL and 191 ng/mL, respectively, at 600 mg QD. The preliminary PK results showed that systemic exposure of HMPL-523 in Australian subjects was lower than that in Chinese subjects, but other PK characteristics in Chinese and Australian subjects were similar.

The plasma concentration of CCI [redacted] were monitored in this study (data on file). The mean ARs of area under the drug concentration-time curve over the dose interval at steady state ($AUC_{tau,ss}$) CCI [redacted] were 3.16 and 1.75, respectively, following multiple 100 to 1000 mg QD or 300 and 400 mg BID doses. The mean CCI [redacted] ratios of $AUC_{tau,ss}$ were approximately CCI [redacted] respectively. The mean

CCI respectively.

Efficacy

As of 10 May 2020, in study 2015-523-00AU1, 61 patients had at least 1 post-baseline tumor assessment, and the objective response rate (ORR) in all enrolled patients was C %, with patients achieved CR, C patients achieved PR/partial response with lymphocytosis (PR-L), C patients achieved SD, C patients experienced progressive disease (PD), and 4 patients not evaluable for best overall response (BOR). CCI patients with FL (at 600 mg QD, at 800 mg QD, and at 400 mg BID) achieved CR, patients with CLL/SLL at 800 mg QD, at 400 mg BID, and escalated from 100 mg QD to 400 mg QD) achieved PR/PR-L, patients with FL (at 600 mg QD, at 800 mg QD, and at 300 mg BID), patients with MZL (at 600 mg QD, at 800 mg QD), and 1 patient with low grade NHL (600 mg QD) achieved PR.

2.2.4.4 Study 2015-523-00CH1 Phase I Study in Patients with Relapsed/Refractory Lymphoma

This study was completed on 30 September 2021. Overall, 134 patients were enrolled in the study. Twenty-seven patients were treated in the dose escalation phase, including 7 patients in the 200-mg QD cohort, 3 patients in the 400-mg QD cohort, 6 patients in the 600-mg QD cohort, 3 patients in the 800-mg QD cohort, and 8 patients in the 200-mg BID cohort. One hundred seven patients were treated in the dose expansion phase, including 32 patients in the 400-mg QD cohort and 75 patients in the 600-mg QD cohort. During the dose expansion phase, RP2D was 600 mg QD for patients whose weight was > 65 kg and 400 mg QD for patients whose weight was ≤65 kg.

Safety

CCI

Pharmacokinetics

CCI on Day 1, Day 15, and Day 28 following multiple 200 to 800 mg QD and 200 mg BID HMPL-523 in the dose escalation phase, and 400 mg QD and 600 mg QD doses in the dose expansion phase, in Chinese patients with relapsed or refractory mature B-cell tumor. In this study, all patients were instructed to take HMPL-523 at approximately 30 minutes after a meal.

Median T_{max} values for HMPL-523 ranged from 3.00 to 5.97 hours following 200 to 800 mg QD doses, and from 1.98 to 3.88 hours following multiple 200 mg BID doses. The mean ARs for AUC_{tau} on Days 15 and 28 ranged from 1.27 to 2.65 following multiple 200 to 600 mg QD doses, and from 1.97 to 2.52 following multiple 200 mg BID doses. In general, lower C_{max}, similar C_{min}, and higher AR for AUC_{tau} were observed with 200 mg BID dosing compared to 400 mg QD dosing.

CCI with the increased HMPL-523 doses from 200 to 800 mg QD and 200 mg BID. Median T_{max} values were similar between QD and BID dosing regimen, generally 4.00 hours post-dose CCI and ranging from 1.93 to 4.08 hours post-dose CCI The mean AR for AUC_{tau} on Days 15 and 28 ranged from 1.22 to

3.25 CCI , and 0.426 to 1.52 CCI , following multiple 200 to 600 mg QD doses, and from 2.40 to 3.34 CCI , and 1.79 to 1.88 CCI following multiple 200 mg BID doses. In general, lower C_{max}, similar C_{min} and higher AR for AUC_{tau} were observed with 200 mg BID dosing compared to 400 mg QD dosing. CCI following multiple 200 to 600 mg QD or 200 mg BID doses.

The relationship between dose levels and exposure (for Day 1: C_{max} and AUC_{0-t}; for Day 15 or Day 28: C_{max}, AUC_{tau}, and C_{min}) of HMPL-523 CCI in dose escalation phase was evaluated by Power Model. Following QD oral administration of HMPL-523, on Days 1, 15 and 28, the 95% CI of the slope for HMPL-523, CCI was not completely included in the reference interval 0.839-1.16 [1+ln (0.8)/ln (800/200) - 1+ln (1.25)/ln (800/200)]. The linear relationship between dose level and the exposure of HMPL-523 and CCI was inconclusive over the dose range of 200 to 800 mg.

Efficacy

A total of 114 patients had at least 1 post-baseline tumor assessment (defined as efficacy-evaluable analysis set, EEAS), including 23 patients in the dose escalation stage and 91 patients in the dose expansion stage.

In the dose escalation stage, tumor responses were observed at the dose levels of 400 to 600 mg QD or 200 mg BID. Four patients with FL and 1 patient with SLL achieved PR, and the investigator-assessed ORR was 21.7% (95% CI: 7.5%, 43.7%) based on the EEAS (N = 23). Of the 5 patients with PRs, median time to response (TTR) was 3.6 months (95% CI: 1.9, -) and median duration of response (DoR) was 11.0 months (95% CI: 4.7, -). Based on the safety set (included patients who had at least 1 dose of study drug, N = 27), median time to tumor progression (TTP) was 8.3 months (95% CI: 1.8, 16.5) and median progression free survival (PFS) was 8.3 months (95% CI: 1.8, 16.5).

In the dose expansion stage, based on the EEAS (N = 91), 5 patients achieved CRs and 33/4 patients achieved PR/PR-Ls, and the investigator-assessed ORR was 46.2% (95% CI: 35.6, 56.9). Of the responders, the median DoR was 13.1 months (95% CI: 6.5, -), and median TTR was 1.9 months (95% CI: 1.9, 2.0). Based on safety set (N = 107), the median PFS was 8.2 months (95% CI: 5.5, 12.0), and median TTP was 8.3 months (95% CI: 5.6-13.8).

Cohort A (CLL/SLL)

Based on the EEAS (N = 16), 1 patient had CR, and 4/4 patients had PR/PR-L, and the investigator-assessed ORR was 56.3% (95% CI: 29.9%, 80.2%). Of the responders, median DoR was 13.1 months (95% CI: 1.8, -) and median TTR was 1.9 months (95% CI: 1.8, 1.9). Based on the safety set (N = 19), median TTP was 14.9 months (95% CI: 3.7, -) and median PFS was 14.9 months (95% CI: 3.7, -).

Among the 12 efficacy-evaluable CLL patients, the ORR was 50.0% (95% CI: 21.1%, 78.9%); among the 4 efficacy-evaluable SLL patients, the ORR was 75.0% (95% CI: 19.4%, 99.4%), and both were assessed by investigator.

Cohort B (DLBCL, FL Grade 3b)

Based on the EEAS (N = 9), 1 and 2 patients achieved CR and PRs, respectively, obtaining an ORR of 33.3% (95% CI: 7.5%, 70.1%), as assessed by the investigator. Among the responders,

median TTR was 1.9 months (95% CI: 1.8, -) and median DoR was 5.3 months (95% CI: 3.7, -). Based on the safety set (N = 14), median TTP was 1.9 months (95% CI: 0.8, 9.1) and median PFS was 1.9 months (95% CI: 0.8, 9.1).

Of the 7 efficacy-evaluable DLBCL patients, the ORR was 28.6% (95% CI: 3.7%, 71.0%). Two FL (Grade 3b) patients had evaluable tumor response, and 1 of them had PR.

Cohort C (MCL)

Based on the EEAS (N = 7), 2 patients had PRs, and the investigator-assessed ORR was 28.6% (95% CI: 3.7%, 71.0%). Among patients with an objective response, median TTR was 1.9 months (95% CI: 1.9, -) and median DoR was 4.6 months (95% CI: 1.9, -). Based on the safety set (N = 10), median TTP was 3.7 months (95% CI: 1.1, -) and median PFS was 3.7 months (95% CI: 0.9, -).

Cohort D [MZL, LPL/WM, and FL (Grades 1, 2, and 3a)]

Based on the EEAS (N = 59), per independent review committee (IRC) assessment, 8 patients had CRs, 22 patients had PRs, and the overall ORR was 50.8% (95% CI: 37.5%, 64.1%). Among patients with an objective response, median TTR was 2.7 months (95% CI: 1.8, 3.7) and median DoR was 15.7 months (95% CI: 7.4, -). Based on the safety set (N = 64), median TTP was 12.0 months (95% CI: 8.2, -) and median PFS was 12.0 months (95% CI: 6.3, -). The investigator-assessed ORR was 47.5% (95% CI: 34.3%, 60.9%), median TTR, DoR, TTP and PFS were 2.0 months (95% CI: 1.9, 3.6), 13.9 months (95% CI: 6.4, -), 11.0 months (95% CI: 6.3, 19.3), and 8.3 months (95% CI: 5.5, 16.6), respectively.

Of the 43 efficacy-evaluable FL (Grades 1, 2, and 3a) patients, per IRC assessment, 7 patients had CRs, and 19 patients had PRs, obtaining an overall ORR of 60.5% (95% CI: 44.4%, 75.0%). Of the responders, the median TTR was 3.6 months (95% CI: 1.8, 3.7) and median DoR was not reached (95% CI: 6.5, -). Of the 47 FL patients in the safety set, median TTP was 12.0 months (95% CI: 8.2, -) and median PFS was 11.0 months (95% CI: 6.3, -). The investigator-assessed results were: ORR, 60.5% (95% CI: 44.4%, 75.0%); median TTR, 1.9 months (95% CI: 1.9, 3.6); median DoR, 14.8 months (95% CI: 6.5, -); median TTP, 12.0 months (95% CI: 6.8, -); and median PFS, 11.0 months (95% CI: 6.3, 16.6).

2.2.4.5 Study 2018-523-00US1 Phase I Study in Patients with Relapsed/Refractory Lymphoma

This ongoing Phase I, open-label study to evaluate the safety, tolerability, PK, and preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma is described in this protocol. The expansion cohorts include HL, CLL/SLL, CLL/SLL (post-BTK), MCL, FL, MZL, WM/LPL, peripheral T-cell lymphomas (PTCL), and cutaneous B-cell lymphoma (CBCL).

A post-BTK exposure cohort in CLL/SLL is being evaluated based on recent experience from the Phase I study of HMPL-523 in China (2015-523-00CH1) indicating efficacy in this patient population. In the dose expansion phase of this study, 19 CLL patients were enrolled with 16 evaluable for response. The ORR in CLL/SLL patients was 56.3%, including 1 CR (6.3%) and 8 PR/PR-L (50%), with a median duration of response (mDoR) of 13.1 months (range: 1.8 - not calculable [NC]) months). In the 8 CLL/SLL patients with prior BTK exposure, the ORR was 50% with median DoR of 14.7 months (95% CI: 1.9, NC) and median PFS of 16.5 months (95% CI: 1.6, NC). Based on this preliminary efficacy and the need for therapies in

CLL/SLL patients who are intolerant of or resistant to BTK inhibitors, the sponsor proposes a larger cohort to evaluate efficacy in CLL/SLL patients who have failed or are intolerant to BTK inhibitors.

Early efficacy in FL was also demonstrated in the 2015-523-00CH1 study. This study enrolled 47 patients with FL, of which 43 were evaluable for response. The ORR was 60.5% (95% CI: 44.4, 75.0) with mDoR of 14.8 months (95% CI: 6.5, -) and median PFS of 11.0 months (95% CI: 6.3, 16.6). As this cohort had the best efficacy in the CH1 lymphoma study, the sponsor proposes a larger cohort to evaluate FL patients.

As discussed in Section 2.1, targeting Syk may be a novel strategy for the treatment of HL.

Safety

CCI

Pharmacokinetics

As of 10 May 2022, preliminary PK data for HMPL-523 and CCI following multiple QD doses from 100 to 800 mg in the dose escalation phase were available. All patients were instructed to take HMPL-523 at approximately 30 minutes after a meal.

There were limited calculable PK parameters at steady state at 800 mg QD; therefore, the data are excluded from the summary described below. Following multiple oral doses of HMPL-523 from 100 to 700 mg QD, the median T_{max} values for HMPL-523 ranged from 3.0 to 6.0 hours post-dose. The exposure of HMPL-523 (maximum plasma concentration at steady state [$C_{max,ss}$] and area under the drug concentration-time curve over the dose interval at steady state [$AUC_{tau,ss}$]) increased in approximately dose-proportional manner over the dose range of 100 to 700 QD. The apparent oral clearance at steady state ranged from 189 to 304 L/h for doses from 100 to 700 mg QD. HMPL-523 reached PK steady state by Day 15. The mean AR was approximately 1.60 (ranging from 1.21 to 2.01) following multiple 100 to 700 mg QD doses.

The exposure of the CCI with increased HMPL-523 doses. Median T_{max} values for CCI ranged from 4.0 to 8.0 hours, and 2.0 to 4.0 hours post-dose, respectively, following multiple doses of 100 to 800 mg QD. The mean ARs of $AUC_{tau,ss}$ CCI were approximately 1.86 and 1.55, respectively. The mean CCI ratios of $AUC_{tau,ss}$ were approximately CCI respectively. The mean CCI ratios of $AUC_{tau,ss}$ were approximately CCI respectively.

Efficacy

As of the data cut-off date (10 May 2022), this study was still ongoing. No efficacy data was available.

2.2.4.6 Study 2018-523-00CH1 Phase I Study in Patients with Primary Immune Thrombocytopenia

This study was completed on 18 April 2022. Overall, 45 patients were enrolled in the study. During 0 to 8 weeks double-blind phase, 34 patients received HMPL-523 and 11 patients

received placebo. During the 16-week open-label phase, 25 patients received study drug and 7 patients received placebo.

Safety

Within 28 days after the first dose in the double-blind period (N = 34 in HMPL-523 cohorts, N = 11 in Placebo cohort), the Grade ≥ 2 treatment-related TEAEs were reported in 2 (8.3%) patients at all dose cohorts of HMPL-523, including hypertriglyceridemia (4.2%) and anemia (4.2%); and in 1 (12.5%) patient of placebo cohort (aspartate aminotransferase increased).

In the 0- to 8-week double-blind period, 34 (100.0%) versus 9 (81.8%) patients reported TEAEs in HMPL-523 versus placebo cohorts, of whom 22 (64.7%) versus 3 (27.3%) patients reported treatment-related TEAEs, and the top 3 preferred terms (PTs) were blood lactate dehydrogenase increased (20.6% versus 9.1%), alanine aminotransferase increased (14.7% versus 9.1%), and amylase increased (14.7% versus 0).

Seven (20.6%) versus 2 (18.2%) patients reported TEAEs of Grade ≥ 3, of whom 3 (8.8%) patients versus none patients reported treatment-related TEAEs of Grade ≥ 3. The treatment-related TEAEs of Grade ≥ 3 in HMPL-523 cohorts were all singly reported, including gamma-glutamyltransferase increased (2.9%), white blood cell count decreased (2.9%), hypertriglyceridemia (2.9%), and hypertension (2.9%).

None versus one (9.1%) patient in HMPL-523 versus placebo cohorts reported TEAEs leading to permanent treatment discontinuation, which included haemorrhage subcutaneous and gingival bleeding in placebo cohort and were not treatment related; none versus one (9.1%) patient reported TEAEs leading to study drug dose reduction or dose interruption, which included alanine aminotransferase increased and aspartate aminotransferase increased in the placebo cohort; both were treatment-related.

Two (33.3%) and 2 (18.2%) patients in the HMPL-523 cohorts (only in 100 mg cohort) and in the placebo cohort, respectively, reported SAEs, none of which were treatment-related. No TEAEs leading to death occurred.

In the 0- to 24-week period for all patients treated with HMPL-523, all 41 patients reported TEAEs, of whom 31 (75.6%) patients reported treatment-related TEAEs, and the top 3 treatment-related TEAEs included aspartate aminotransferase increased (29.3%), alanine aminotransferase increased (26.8%), and blood lactate dehydrogenase increased (22.0%).

Nine (22.0%) patients reported TEAEs of Grade ≥ 3 in HMPL-523 cohorts, and of them, 3 (7.3%) patients reported treatment-related TEAEs of Grade ≥ 3, which were all singly reported, including gamma-glutamyltransferase increased (2.4%), white blood cell count decreased (2.4%), hypertriglyceridemia (2.4%), and hypertension (2.4%).

No patients treated with HMPL-523 reported TEAEs that led to permanent discontinuation of study drug. Three (7.3%) patients reported TEAEs leading to dose reduction or interruption of study drug, which were singly reported and not related to treatment.

Five (12.2%) patients reported SAEs, which were not related to treatment. No deaths were reported during this period.

Pharmacokinetics

The PK of HMPL-523 in this Phase I Study 2018-523-00CH1 has been characterized on Day 15 following multiple 100 to 400 mg QD doses in the dose escalation phase and 300 mg QD doses in the dose expansion phase in Chinese patients with ITP. All patients were instructed to take HMPL-523 at approximately 30 minutes after a meal.

Following multiple oral doses of HMPL-523 from 100 to 400 mg QD, the median T_{max} value for HMPL-523 was 4.0 hours post-dose. The systemic exposure ($C_{max,ss}$ and $AUC_{tau,ss}$) increased in a dose proportional manner across the dose range of 100 to 400 mg QD. The geometric mean $C_{max,ss}$, maximum plasma concentration at steady state, and $AUC_{tau,ss}$ of HMPL-523 following the RP2D 300 mg QD were 163 ng/mL, 41.3 ng/mL, and 2070 h·ng/mL, respectively. The apparent oral clearance (CL_{ss}/F) at steady state on Day 15 ranged from 130 to 173 L/h.

[redacted] Median T_{max} values [redacted] ranged from 3.0 to 4.0 hours, and 1.5 to 2.0 hours post-dose, respectively, following multiple doses of 100 to 400 mg QD HMPL-523. The mean [redacted] ratio of $AUC_{tau,ss}$ [redacted] and [redacted] respectively.

Efficacy

HMPL-523 300 mg QD showed a preliminary efficacy in patients with ITP, with a high response rate (patients with platelet count $\geq 50 \times 10^9$/L at least once) and durable response rate (patients with platelet count $\geq 50 \times 10^9$/L in at least 4 of the last 6 scheduled visits) of 80.0% and 40.0%, respectively, in all patients treated with HMPL-523. For patients who have received prior thrombopoietin or thrombopoietin receptor agonists, the response rate and durable response rate were also 80.0% and 40.0%, respectively.

2.2.4.7 Study 2020-523-00CH1 Phase III Study in Patients with Primary Immune Thrombocytopenia

This is an ongoing Phase III, randomized, double-blind, placebo-controlled study of safety and efficacy of HMPL-523 in patients with ITP. This study includes 2 stages: a double-blind treatment stage (Stage 1) and an open-label treatment stage (Stage 2). As of 10 May 2022, the study was still ongoing and blind. Nine (9) patients have completed the double-blind treatment and entered open-label treatment.

Safety

Four (44.4%) patients reported TEAEs, of them 3 (33.3%) patients reported treatment-related TEAEs, which included alanine aminotransferase increased (22.2%) and aspartate aminotransferase increased (22.2%) which were reported in ≥ 2 patients. No TEAEs of Grade ≥ 3 reported.

Efficacy

As of 10 May 2022, this study is still ongoing and blinded; no efficacy data were available.

2.2.4.8 CCI [redacted]

[redacted] patients reported at least 1 TEAE, of whom, [redacted] patients reported at least 1 treatment-related TEAE. The top 3 treatment-related TEAEs included AST increased [redacted], ALT increased [redacted], and neutrophil count decreased [redacted]

[redacted] patients reported TEAE of Grade ≥ 3, of whom, [redacted] patients reported at least 1 treatment-related TEAE of Grade ≥ 3. The top 3 treatment-related TEAEs of Grade ≥ 3 included neutrophil count decreased [redacted] pneumonia [redacted], and white blood cell count decreased [redacted]

[redacted] patients out of a total of 233 patients, who received HMPL-523 mono-therapy treatment in studies 2015-523-00AU1, 2015-523-00CH1, and 2018-523-00US1 reported SAEs. [redacted] patients reported treatment-related SAEs, and the top 3 PTs with highest incidence included pneumonia ([redacted] patients), interstitial lung disease ([redacted] patients), and febrile neutropenia ([redacted] patients).

As of 10 May 2022, [redacted] fatal SAEs were reported in Study 2015-523-00AU1, 5 fatal SAEs were reported in Study 2015-523-00CH1, and 1 fatal SAE was reported in Study 2018-523-00US1.

2.3 Study Rationale and Benefit-Risk Assessment

2.3.1 Study Rationale

SYK is a member of the SYK/zeta-associated protein 70 family and is a nonreceptor intracellular tyrosine kinase. In hematopoietic cells, SYK is recruited to the intracellular membrane by activated membrane receptors like the BCR or Fc receptor and then binds to the intracellular domain of the receptors. SYK is activated after phosphorylation by Src family kinases and then further induces downstream intracellular signals including BLNK, phosphoinositide 3'-kinase δ (PI3Kδ), BTK and phospholipase C γ2 (PLCγ2) to regulate B-cell proliferation, growth, differentiation, homing, survival, maturation, and immune responses.

In vitro experiments have also demonstrated that the SYK molecule plays a major role in B-NHLs. For example, down-regulation of SYK reduced the proliferating signal as well as the expansion of DLBCL cells and spontaneous lymphoma cells from transgenic mice (Cheng et al 2011). These experiments indicate that over-activated SYK plays an important role in promoting the activation of B-NHLs. Therefore, inhibition of SYK activation in B-NHLs may block signal transduction, resulting in inhibition of B-cell lymphoma proliferation or induction of tumor cell apoptosis.

Clinical data have shown that SYK is abnormally activated in B-cell lymphomas. SYK downstream of the BCR was highly expressed and phosphorylated in CLL cells isolated from the

peripheral blood of patients (Hoellenriegel et al 2012). Phosphorylated SYK was positive in approximately 44% of patients with DLBCL patients (Cheng et al 2011).

Some SYK inhibitors, such as fostamatinib (prodrug of R406) and entospletinib (GS-9973), have shown encouraging activity in clinical trials against NHLs with tolerable toxicity (Friedberg et al 2010, Sharman et al 2017).

The repertoire of cells in which SYK functions as a pro-survival factor extends to hematological malignancies not of B-cell origin (a variety of T cell lymphomas) in which it is likely that immunoreceptor tyrosine-based activation motif-containing receptors other than the BCR are coupled to the activation of SYK (Hahn et al 2009). The expression of SYK can be detected in 94% of PTCLs, and immunoblotting experiments indicate that the kinase is constitutively phosphorylated in these cells. These data indicate that exploring SYK inhibitors in these tumor types is reasonable.

A total of 68 patients with relapsed and refractory lymphomas were enrolled and treated with fostamatinib as a single agent in a Phase I/II study. The ORRs were reported at 22% (5 of 23) for DLBCL, 10% (2 of 21) for FL, 55% (6 of 11) for SLL/CLL, and 11% (1/9) for MCL (Friedberg et al 2010).

A total of 61 patients with relapsed and refractory CLL were treated with fostamatinib as a single agent in a Phase II study. The median PFS was 16.6 months, 16.8 months, and 16.4 months for the 100-, 200-, and 400-mg groups, respectively. The ORR was 28%, 43%, and 61% for the 100-, 200-, and 400-mg groups, respectively (Sharman et al 2017).

The most common adverse effects observed in clinical studies of fostamatinib and entospletinib were diarrhea, hypertension, fatigue, and bone marrow toxicities. These TEAEs are manageable and reversible. These results suggest that the SYK inhibitor may represent a class of safe and effective drugs to treat B-cell lymphomas.

2.3.2 Benefit-Risk Assessment

2.3.2.1 Risk Assessment

Important Identified Risks

Hepatotoxicity

Increases in hepatic enzymes (ALT, AST, bilirubin, alkaline phosphatase [ALP], and gamma-glutamyl transferase) have been observed in animals and humans treated with HMPL-523, and are known adverse reactions of other SYK inhibitors (Sharman et al 2015) (TavalisseTM Prescribing Information 2018). Patients with a history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with hepatitis B or C virus should be excluded from clinical trials.

Additionally, patients should be excluded if screening AST and/or ALT are > 2.5 × upper limit of normal (ULN), or if screening total blood bilirubin > 1.5 × ULN. Liver function tests should be performed with each site visit. HMPL-523 should be withheld in the event of any ≥ Grade 3 adverse event (AE) indicative of hepatic injury.

Respiratory Tract Infections

Respiratory tract infections, including pneumonia have been reported in patients treated with HMPL-523, some of which have been life-threatening or fatal. Patients should be excluded from clinical trials with HMPL-523 if screening absolute neutrophil count (ANC) < 1.5×10^9/L. Complete blood cell count (CBC) should be performed at the beginning of each cycle. Prophylactic antibiotics, symptomatic, and supportive treatments should be administered per standard practice.

2.3.2.2 Benefit Assessment

HMPL-523 is a highly selective SYK inhibitor with a different structure compared with fostamatinib and entospletinib. In most in vitro nonclinical studies, HMPL-523 inhibited SYK kinase with inhibitory activity comparable to that of fostamatinib and entospletinib and has superior selectivity against the kinase insert domain receptor to fostamatinib. In Phase I studies of HMPL-523 in patients with hematologic malignancies in both Australia and China, HMPL-523 was well tolerated at doses of up to 600 mg QD. HMPL-523 also demonstrated efficacy in patients with hematologic malignancies in these studies. Refer to Section 2.2.4 for details of safety and efficacy results in completed and ongoing HMPL-523 clinical studies.

2.3.2.3 Overall Benefit-Risk Conclusion

Overall, the nonclinical data and early clinical data suggest that HMPL-523 is a selective SYK inhibitor with a good nonclinical PK and toxicological profile. The nonclinical and preliminary clinical data suggest that HMPL-523 should be evaluated as a potential therapeutic agent for patients with lymphoma in the US.

3 OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety and tolerability of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage
- To determine the MTD/RP2D and characterize the DLTs associated with HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage
- To evaluate the preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma in the dose expansion stage

3.2 Secondary Objectives

- To characterize the PK properties of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage and the dose expansion stage
- To evaluate the safety and tolerability of HMPL-523 at the MTD/RP2D in patients with relapsed or refractory lymphoma in the dose expansion stage
- To evaluate the preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage

3.3 Exploratory Objectives

- To evaluate the PK properties of CCI [redacted] HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation and dose expansion stages
- To explore biomarkers for PD, predictive, and others (not exhaustive), including antitumor activities of HMPL-523

4 STUDY DESIGN

4.1 Description of Study

This is a Phase I, open-label, multicenter study of HMPL-523 administered orally to patients with relapsed or refractory lymphoma who have exhausted approved therapy options.

The study consists of a dose escalation stage (Stage 1) and a dose expansion stage (Stage 2). Both stages include a screening period, a treatment period, and a follow-up period. The screening period starts when the patient has provided written informed consent and ends immediately prior to initiation of study drug administration on Day 1 of Cycle 1. The treatment period begins on Day 1 of Cycle 1 and concludes on the final day of study drug administration. The follow-up period begins at the end of treatment and continues until the patient experiences disease progression, starts a new anticancer therapy, or dies, or the sponsor has concluded the study.

The start of the clinical study is defined as the date the study is open for recruitment at any site. This date was 21 February 2019. The start of the clinical study in EU is defined as the date the clinical study is open for recruitment at the first clinical study site within an EU Member State. This date was 05 September 2019.

4.2 Dose Escalation Stage (Stage 1)

Starting Dose and Rules for Dose Escalation

Dosing will begin at 100 mg QD. A cycle of study treatment will be defined as 28 days of continuous dosing. The modified 3 + 3 design will be applied for dose escalation and MTD determination to limit the number of patients being exposed to potentially ineffective or unsafe doses. The study will enroll 1 patient, and the patient will be treated for a 28-day cycle in the initial dose cohort. If there is no DLT and no more than 2 TEAEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 in the first treatment cycle, the study will be escalated to the next dose cohort and continue with the standard 3+3 design. Otherwise, the trial will revert to a standard 3+3 design from the initial dose cohort.

A minimum of 3 patients will be enrolled and observed for toxicity in each successive dose cohort after the initial dose cohort. If the 3 patients initially enrolled in a given dose cohort complete the DLT assessment window (Cycle 1, Days 1-28) without experiencing a DLT, 3 patients will be enrolled at the next higher dose level. If 2 or more of the initial 3 patients enrolled at any dose level experience a DLT during the DLT assessment window, the dose escalation will be halted. If 1 of the initial 3 patients enrolled at any dose level experiences a DLT during the DLT assessment window, additional patients will be enrolled at that dose level for a minimum of 6 evaluable patients for DLT. If a DLT is observed in 1 of the 6 evaluable patients at this dose level, dose escalation will proceed to the next pre-defined dose level. If DLTs are observed in 2 or more of the 6 evaluable patients at a given dose level, the dose escalation will be halted. If the dose escalation is completed due to 2 or more DLTs at a dose level and that dose level is ≥ 50% higher than the previous dose level, then an intermediate dose level may be evaluated for toxicity in the same manner as described above. If the dose level is <50% higher than the previous dose level, in which only 3 DLT evaluable patients were enrolled, 3 additional patients will be enrolled at that dose level to comprise 6 DLT evaluable patients.

See Table 1 below for the proposed dose escalation scheme.

Table 1 Proposed Dose Escalation Scheme

Cohort	Dose	Route of Administration
1	100 mg QD	Orally, with water, after meal
2	200 mg QD	Orally, with water, after meal
3	400 mg QD	Orally, with water, after meal
4	600 mg QD	Orally, with water, after meal
5	800 mg QD	Orally, with water, after meal

Abbreviation: QD = once daily.

The need for dose escalation to a specific dose beyond 800 mg QD, or de-escalation specifically to 700 mg QD, will be evaluated jointly by the investigators and the sponsor based on the cumulative clinical safety, PK, and preliminary efficacy data.

Safety monitoring and evaluation of dose escalation will be carried out by the Safety Review Committee (SRC), which will comprise the sponsor's study team members (including the medical monitor, the safety monitor, and others as deemed necessary) and the principal investigators of the study sites. Safety data will be evaluated and reviewed by the SRC to determine if the assigned HMPL-523 dose is safe to continue for dose escalation or to de-escalate to the lower dose level.

4.3 Intrapatient Dose Escalation

Intrapatient 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 also has been cleared of DLT (safe and tolerable), prior to the start of that intrapatient dose escalation.

4.4 Definition of a Dose-Limiting Toxicity

DLTs are defined as the occurrence in the DLT assessment window (see Section 4.4.1) of any of the following TEAEs, unless they are clearly unrelated to the study drug:

a. Nonhematologic toxicity: All nonhematologic TEAEs of Grade 3 or greater with the exception of:
   i. Grade 3 nausea, vomiting controlled by supportive therapy

b. Hematologic toxicity:
   i. Grade 4 neutropenia lasting more than 5 days.
   ii. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or any requirement for platelets transfusion.
   iii. Grade 3 or greater 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 unexplained by underlying disease.

c. Any TEAE requiring a dose delay of ≥ 15 days.
d. Any case of Hy's Law.

4.4.1 Dose-Limiting Toxicity Assessment Window

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

4.4.2 Definition of Dose-Limiting Toxicity Evaluable Patient

For decisions on dose escalation, each dose cohort shall present protocol-required number of DLT evaluable patients. A patient 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 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 dose escalation evaluations.

4.4.3 Dosing Beyond Cycle 1

Patients who complete the DLT assessment window (Cycle 1 Days 1-28) and are deemed by the investigator to be benefiting from treatment with HMPL-523 may continue treatment with HMPL-523 until disease progression, intolerable toxicity, at investigator's assessment that the patient is no longer benefiting from the study treatment, patient withdrawal from the study, the end of the study, or death. Conversely, if in the opinion of the attending principal investigator the patient may have 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 intrapatient dose escalation (Section 4.3). If the study is terminated or ends before a patient reaches any of these endpoints, refer to Section 5.3.5.

4.4.4 Definition of Maximum Tolerated Dose

The MTD is defined as the maximum dose at which no more than 16.7% patients in a single cohort experiences a DLT in the first cycle (Cycle 1 Days 1-28).

4.4.5 Definition of Recommended Phase II Dose

The decision regarding the RP2D was based on the following considerations:

- MTD if reached
- PK with or without associated safety and preliminary efficacy findings

These criteria constituted the basis for RP2D determination that was agreed by both the sponsor and the investigators.

Based on evaluation of data collected during the dose escalation phase, the RP2D has been determined to be 700 mg once daily.

4.5 Dose Expansion Stage (Stage 2)

The safety, tolerability, PK, and preliminary efficacy of HMPL-523 at the MTD/RP2D, which has been determined to be 700 mg once daily, will be further evaluated in patients with relapsed or refractory non-Hodgkin's and Hodgkin's lymphomas.

Amendment 4:

As described in Amendment 4, based on strategic evaluation of the development of HMPL-523, the selected lymphoma cohorts were closed as of 30 November 2022: MCL, FL, MZL, WM/LPL, PTCL, and CBCL. Enrollment was continued in the CLL and HL cohorts.

The number of patients enrolled in each cohort as of Amendment 5 is shown in Table 2.

Amendment 5

The last patient was enrolled on CCI [redacted]. Upon implementation of Protocol Amendment 5, a total of 48 patients were enrolled in the dose-expansion portion at the time of enrollment closure, and approximately 3 patients total were on study treatment (Table 2).

Table 2 Dose Expansion Cohorts

Disease Cohort	Enrollment as of Amendment 4 (Approximate)	Enrollment as of Amendment 5 (Approximate)
HL	25	25
CLL	1	1
CLL post BTK**	6	7
Follicular lymphoma	2	2
Mantle cell lymphoma	2	2
Marginal zone lymphoma	1	1
Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma	1	1
PTCL	9	9
CBCL	0	0

Abbreviations: BCL-2 = B-cell lymphoma-2; BTK = Bruton tyrosine kinase; CBCL = cutaneous B-cell lymphoma; CLL =chronic lymphocytic leukemia; HL = Hodgkin's lymphoma; PTCL = peripheral T-cell lymphoma.
**Approximately 10 patients in the CLL post-BTK cohort will have prior BCL-2 inhibitor therapy.

Patients will receive HMPL-523 at the MTD/RP2D, which has been determined to be 700 mg once daily, in every 28-day treatment cycle 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 the study, whichever comes first.

4.6 End of Study

The end of the study is defined as the date on which all patients have their last visit or 2 years after the last patient has his/her first visit, whichever comes first.

4.7 Rationale for Study Design

4.7.1 Rationale for the Starting Dose and the Dose Schedule

As of the data cutoff date of 10 May 2022, HMPL-523 has completed a Phase I dose escalation study in healthy volunteers in Australia (https://clinicaltrials.gov/ct2/show/NCT02105129), a Phase Ib double-blind study in patients with primary ITP in China (https://clinicaltrials.gov/ct2/show/NCT03951623), a Phase I combo-therapy study in patients with AML in China (https://clinicaltrials.gov/ct2/show/NCT03483948), and a dose escalation and expansion Phase I trial in patients with relapsed/refractory lymphoma in China (https://clinicaltrials.gov/ct2/show/NCT02857998).

In the US and EU, HMPL-523 has successfully completed dose escalation at various centers (https://clinicaltrials.gov/ct2/show/NCT03779113).

Safety data from completed dose escalation cohorts of ongoing Phase I clinical trials in both China and Australia show that HMPL-523 is tolerable.

The exposures (AUC and C_{max}) of HMPL-523 at steady state in both the Australian and Chinese studies increased with the dose increase from 100 to 800 mg.

The minimum effective dose in patients with hematologic malignancies was expected to be approximately 600 mg QD.

Table 3 summarized the human PK data of HMPL-523 at steady state at 200 and 400 mg QD in 2 clinical trials as well as the animal toxicokinetic data at the CCI in the 4-week and 13-week toxicity studies. In addition, the free exposures ($AUC_{tau,u}$ and $C_{max,u}$) were also calculated with the free fraction values in human, rat, and dog plasma. Overall, the exposures of HMPL-523 were lower in Australia than in China. For 100 mg QD, based on the free exposures (AUC), the safety window is approximately [redacted] fold and [redacted] fold when based on the CCI of the 13-week toxicity studies in dogs and rats, respectively.

Table 3 HMPL-523 PK and Toxicokinetic Summary

Study	Dose	Parameters				
		f_{up}	AUC_{tau} (h•ng/mL)	$AUC_{tau,u}$ (h•ng/mL)	C_{max} (ng/mL)	$C_{max,u}$ (ng/mL)
2015-523-00AU1	100 mg QD	0.17	372	63.2	27.1	4.61
	200 mg QD	0.17	536	91.1	44.4	7.55
	400 mg QD	0.17	1430	243	101	17.2
2015-523-00CH1	200 mg QD	0.17	1065	181	88.1	15.0
	400 mg QD	0.17	3101	527	224	38.1
4-week toxicity in rats	[redacted] mg/kg	CCI				
13-week toxicity in rats	[redacted] mg/kg	CCI				
4-week toxicity in dogs	[redacted] mg/kg	CCI				
13-week toxicity in dogs	[redacted] mg/kg	CCI				

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; f_{up} = free fraction values; PK = pharmacokinetic; QD = once daily.
Note: All PK and toxicokinetic data shown here were gender-combined.

In summary, nonclinical toxicity studies and 3 Phase I dose escalation trial data provided sufficient rational to set 100 mg/day as the initial dose in this Phase I clinical trial.

4.7.2 Rationale for Selection of Patient Population

The clinical data have indicated that SYK is abnormally activated in B-cell lymphomas. In vitro experiments have also demonstrated that the SYK molecule plays a major role in the activation and proliferation of B-NHLs as abovementioned in Section 2.3. For example, down-regulation of SYK was able to reduce proliferating signal as well as expansion of DLBCL cells and spontaneous lymphoma cells from transgenic mice (Cheng et al 2011). These experiments indicate that over-activated SYK plays an important role in promoting the activation of B-NHLs. Therefore, inhibition of SYK activation in B-NHLs may block signal transduction, resulting in inhibition of B lymphoma cell proliferation or induction of tumor cell apoptosis. This approach may provide a powerful tool for the treatment of B-cell lymphomas.

The patient population of Stage 1, ie, patients with relapsed or refractory lymphoma who have exhausted approved therapy options (as defined in Section 5.1.1), is selected because these patients have exhausted all options offered by the standard of care. Based on the previous clinical data of HMPL-523 in a similar population, HMPL-523 might be offered as an alternative to these patients. The inclusion criterion of the Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 has been selected to make it easy to attribute toxicities to disease or the introduction of this agent.

Patients with relapsed or refractory CLL/SLL, MCL, FL, MZL, PTCL, CBCL, WM/LPL, HL, and CLL post-BTK exposure are selected for Stage 2 because the nonclinical and clinical data, which is mentioned in Sections 2.2 and 2.3, suggest that patients with these types of lymphoma are more likely to be benefit from the treatment of the SYK inhibitor.

Due to strategic evaluation of HMPL-523 development in the US and EU, Protocol Amendment 4 will close enrollment to all NHL expansion cohorts (MCL, FL, MZL, WM/LPL, PTCL, and CBCL). This decision was not due to any patient safety or efficacy concerns related to HMPL-523 therapy. Expansion cohorts for CLL and HL will continue to enroll.

4.8 Outcome Measures

4.8.1 Primary Safety Outcome Measure

- Incidence of DLTs by National Cancer Institute (NCI) CTCAE v5.0 grade and associated dose of HMPL-523

4.8.2 Secondary Safety Outcome Measures

- Incidence of TEAEs by NCI CTCAE v5.0 grade and associated dose of HMPL-523
- Incidence of Grade 3 and 4 abnormalities in safety-related laboratory parameters and associated dose of HMPL-523
- Incidence of TEAEs leading to HMPL-523 dose interruption, reduction, or treatment discontinuation

4.8.3 Pharmacokinetic Outcome Measures

- C_{max}
- T_{max}
- Area under the concentration-time curve in a selected time interval (AUC_{0-t})
- Area under the concentration-time curve during 1 dosing interval (AUC_{tau})
- Apparent clearance (CL/F)
- Minimum plasma concentration (C_{min})
- CCI
- AR

4.8.4 Efficacy Outcome Measures

- ORR is defined as the proportion of patients who have a BOR of CR or PR. The BOR in an individual patient is the best response recorded from the start of treatment until progression or the date of any further anticancer therapy, whichever comes first.
- DoR is defined as the time from when the first response (CR or PR) was achieved until the first documentation of definitive disease progression or death from any cause, whichever occurs first.
- TTR is defined as the time from the date of the first dose of the study drug to first response (CR or PR).
- PFS is defined as the time from the date of the first dose of the study drug until the date of disease progression or death due to any cause.

Efficacy in different subgroups will be evaluated according to specified guidelines/criteria:

- Chronic lymphocytic leukemia: the modified International Workshop on CLL guideline (modified International Workshop on Chronic Lymphocytic Leukemia [IWCLL] 2008, see Appendix 4)
- WM/LPL: consensus of international workshops on WM (IWWM-7 Consensus, see Appendix 5)
- Lymphomas other than CLL or WM/LPL: Lugano Response Criteria for Hodgkin and NHL (Cheson et al 2014, see Appendix 6)

5 MATERIALS AND METHODS

5.1 Patients

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. ECOG performance status of 0 or 1.
4. Histologically confirmed lymphoma, including HL and NHL.

   In the dose expansion stage, the tumor types may be restricted to any or all of the following tumor types. There may be approximately 10 patients in each cohort depending on response signals suggesting efficacy, except for HL cohort with 25 patients and 2 identified cohorts with approximately 20 patients per cohort: relapsed or refractory CLL/SLL (n = 10), and CLL/SLL post-BTK exposure (n = 20), MCL, FL (Grade 1-3a) (n = 20), MZL, WM/LPL, PTCL, and CBCL. As of Amendment 5, the study was closed to new enrollment.

5. Patients with relapsed or refractory lymphoma who have exhausted all approved therapy options as defined below:

   a. Refractory to any prior regimen, defined as no response (CR or PR) to previous therapies, or progression within 6 months of completion of the last dose of prior therapy.
   b. Those who can no longer tolerate/withstand cytotoxic chemotherapy and/or available standard of treatment/care. Where safety profile and risks of toxicity of other treatment options far outweigh any possible clinical benefit.
   c. Those with no curative standard of treatment or where available treatments are not reasonable or do not make sense. In particular, in the opinion of the attending primary investigator, those who will benefit from a new class of compound with a different mechanism of action.
   d. Patients enrolled in the post-BTK CLL cohort should have either disease progression or intolerance to prior BTK inhibitor therapy to enroll. Approximately 10 out of the 20 patients in this cohort should also have disease progression or intolerance to prior BCL-2 (venetoclax or BCL-2 inhibitor on clinical trial) exposure.

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, HL, or SLL is defined as at least 1 bi-dimensionally measurable lesion (nodal disease > 1.5 cm, non-nodal disease > 1 cm in its longest dimension by computed tomography [CT] scan), as defined in Appendix 6.

7. Availability of tumor sample for patients in dose expansion cohorts: This may be an archival tissue sample obtained after most recent therapy or a fresh biopsy; if tumor sample is not available, the sponsor may waive the requirement after discussion

8. Expected survival of more than 24 weeks as determined by the investigator.

9. Patients with prior treatment with any SYK inhibitors (eg, fostamatinib) are eligible for escalation stage 1. However, during expansion stage 2, only patients who discontinue SYK inhibitors for reasons other than disease progression are eligible.
10. Male patients must agree to use a condom and female patients of child-bearing potential must agree to use highly effective contraceptive measures for 30 days after the last dose of study drug. These highly effective contraceptive measures, as defined by the Clinical Trials Facilitation Group, include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine contraceptive device, intrauterine hormone release system, bilateral tubal occlusion, or a vasectomized partner, provided that male partner is the sole sexual partner of the female patient. Postmenopausal females (women who have not had menses for at least 1 year without an alternative medical cause) are exempt from this criterion.

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 lymphoma.
2. Any of the following laboratory abnormalities:

   a. Absolute neutrophil count $<1.0\times10^9$/L
   b. Hemoglobin <80 g/L
   c. 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 believed to be splenic involvement or bone marrow infiltration. The investigator will discuss the eligibility of such patients with the sponsor, and only upon approval (confirmed in writing) by the sponsor will a patient with cell counts below the thresholds be enrolled in the study.

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

3. Inadequate organ function, defined by the following:

   d. Total bilirubin >1.5 × ULN with the following exception:

      - Patients with known Gilbert's disease who have serum bilirubin level ≤ 3 × ULN and normal AST and ALT may be enrolled.

   e. AST and/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.

   f. 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

g. Serum amylase or lipase > ULN
h. International normalized ratio (INR)>1.5 × ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN

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 (confirmed in writing) by the sponsor will a patient with impaired kidney function due to underlying disease be enrolled in the study.

4. Patients with clinically detectable second primary malignant tumors at enrollment or other malignant tumors within the last 2 years (with the exception of radically treated basal cell or squamous cell carcinoma of the skin, in situ cervix, or in situ breast cancer).
5. Any anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, vaccine, or radiotherapy, within 3 weeks prior to the initiation of study treatment.
6. Herbal therapy within 1 week prior to the initiation of study treatment (3 weeks for St. John's wort).
7. Prior administration of radioimmunotherapy within 3 months before the initiation of study treatment.
8. Use of strong CYP3A4 inhibitors or inducers and substrates of CYP3A4, CYP2B6, or CYP1A2, which are identified as narrow therapeutic drugs, within 14 days prior to the initiation of study treatment (refer to Appendix 7).
9. AEs from prior anticancer therapy that have not resolved to Grade ≤1, except for alopecia.
10. Prior autologous stem cell transplant within 6 months prior to the initiation of study treatment.
11. Prior allogeneic stem cell transplant within 6 months prior to the initiation of study treatment or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to the initiation of study treatment.
12. Clinically significant active infection (eg, pneumonia) and interstitial lung diseases: see Appendix 14 for coronavirus disease 2019 (COVID-19) risk assessment and vaccine guidance.
13. Major surgical procedure within 4 weeks prior to the initiation of study treatment.
14. 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 or presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [HBcAb]) or HCV antibody.
– Patients who test positive for HBcAb are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.
– Patients who are positive for HCV serology are only eligible if test result for HCV ribonucleic acid (RNA) is negative.
– CMV antibody will be tested at screening, and if positive, viral load will be determined. Patients who are positive for CMV antibody are only eligible if the test result for CMV DNA is negative.

15. Pregnant (positive serum beta human chorionic gonadotropin [β-HCG] or urine test) or lactating women.
16. New York Heart Association Class II or greater congestive heart failure.
17. Congenital long QT syndrome or corrected QT interval with Fridericia (QTcF) > 480 msec.
18. Current use of medication known to cause QT prolongation or Torsades de Pointes (see full list in Appendix 16).
19. History of myocardial infarction or unstable angina within 6 months prior to the initiation of study treatment.
20. History of stroke or transient ischemic attack within 6 months prior to the initiation of study treatment.
21. Inability to take oral medication, prior surgical procedures affecting absorption, or active peptic ulcer disease.
22. Treatment in a clinical study within 30 days prior to the initiation of study treatment.
23. Ongoing psychiatric disorders, in particular, patients with depression and/or suicidal tendencies.
24. Patients with pathological or organic fractures, in particular, those of unknown etiology.
25. 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, may affect the interpretation of the results, or renders the patient at high risk from treatment complications.

5.2 Method of Treatment Assignment

This is a multicenter, open-label study to evaluate the safety, tolerability, PK, and preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma. Patients will be assigned to dose levels sequentially in the dose escalation stage. In the dose expansion stage, patients will be assigned by the sponsor. Upon completion of all screening evaluations and verification that the patient has met all eligibility criteria, the sites will contact the sponsor to confirm patient eligibility.

5.3 Study Treatment

5.3.1 Formulation, Packaging, and Handling

Three strengths of HMPL-523 tablets (100, 150, and 200 mg based on the free base) will be used for clinical studies. The drug products are tablets that are packaged in white high-density polyethylene bottles. The tablets are composed of widely used pharmaceutical excipients (United States Pharmacopeia grade or equivalent) and HMPL-523 CCI drug substance. The tablets should be stored below 25°C.

For further details, see the HMPL-523 IB.

5.3.2 Drug Labeling

The investigational drug will be labeled as required by local regulations.

5.3.3 Drug Accountability

All study drugs required for this study will be provided by HUTCHMED Limited or the authorized 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 study drugs received by, dispensed from, and returned to the study site will be recorded in the source documentation.

The study drug will be disposed of at the study site according to the study site's institutional standard operation procedure and local regulations with the appropriate documentation upon approval of sponsor.

5.3.4 Dosage, Administration, and Compliance

Dose levels to be potentially tested in this study include 100, 200, 400, 600, and 800 mg/day orally.

The proposed dose of HMPL-523 is as specified in HMPL-523 should be taken with approximately 8 ounces (240 mL) of water under fed conditions, ideally within 30 minutes after meal but not later than 90 minutes after a meal (Table 1). Patients are advised to take QD dosage as required in cohorts/groups. All efforts should be made to ensure that the patient takes HMPL-523 at approximately the same time every day during their participation in the study and ideally within a ±4-hour window.

HMPL-523 should be taken with approximately 8 ounces (240 mL) of water under fed conditions, ideally within 30 minutes after meal but not later than 90 minutes after a meal (Table 1). The administration time should be accurately recorded in the patient diary.

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Sections 5.4 and 5.7.

Any overdose or incorrect administration of the study drug should be noted on the patient's source documentations and case report form (CRF). AEs associated with an overdose or incorrect administration of the study drug should be recorded on the patient's source documents and the AE page of the CRF.

5.3.5 Post-Trial Access to HMPL-523

The sponsor does not have any scheduled plans to provide HMPL-523 or any other study interventions for patients after the end of the study or for any patient who discontinues or withdraws from the study.

The sponsor will evaluate whether to continue providing HMPL-523 after the study is complete. In the event that the sponsor deems post-trial access to HMPL-523 to be appropriate, the sponsor may offer post-trial access to the HMPL-523 free of charge to eligible patients as outlined below.

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

- The patient has relapsed/refractory lymphoma that requires continued study drug treatment for his or her wellbeing.
- 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 the study drug after the end of the study if any of the following conditions are met:

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

5.4 Dose Delays and Modification

5.4.1 During Dose-Limiting Toxicity Assessment Window

If a patient experiences a TEAE of Grade 3 or Grade 4 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy will be administered as required in accordance with local practices/guidelines.

Patients who experience a DLT may resume dosing at the same or the previous lower dose level at the discretion of the investigator if the toxicity is resolved or improved to baseline level. If a patient experiences an unacceptable toxicity at the reduced dose level, he/she will be discontinued from treatment. No patient will have his/her dose reduced by more than 2 dose levels. Once dose is reduced, it cannot be re-escalated.

If a clinically significant TEAE or unacceptable toxicity that does not meet the definition of a DLT is observed, the patient may receive subsequent doses to complete the dosing schedule, provided that the TEAE is improved to CTCAE Grade ≤2 within 2 weeks.

Dose reduction in patients without DLT is not permitted in the DLT assessment window without the sponsor's approval.

5.4.2 After Dose-Limiting Toxicity Assessment Window in Stage 1 or in Stage 2

After the DLT assessment window in Stage 1 or in Stage 2, the dose of HMPL-523 may be interrupted and/or reduced to the next lower dose level (600 mg) if any of the following are observed:

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 nonhematologic toxicity (except for alopecia and skin eruption, nausea, vomiting, diarrhea, or constipation if well-controlled by systemic or topical medication)

Treatment with HMPL-523 should be withheld until the toxicity resolves to CTCAE Grade ≤2. Dosing may then be resumed at either the same dose level or the previous lower dose level if the toxicity is improved to CTCAE Grade ≤2 within 2 weeks at the investigator's discretion. Consult with the sponsor if a treatment hold longer than 2 weeks is required for recovery from toxicity. If treatment is resumed at the same dose and the patient experiences the same toxicity over Grade 2, the dose should be reduced (600 mg) after resolution of the event. If the dose is reduced in Stage 2, additional PK sampling will be required at steady state (please refer to Appendix 3 and Section 5.9.1). If the patient continues to experience unacceptable toxicity, a second dose reduction (400 mg) is permitted. Every patient is allowed to reduce dosing levels of HMPL-523 only twice. If a patient continues to experience unacceptable toxicity after 2 dose reductions, or if HMPL-523 dosing is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor.

5.4.3 Recommendations for Management of Toxicity Including Dose Modification

Recommendations for management of identified toxicities (pulmonary toxicities [including pneumonia/pneumonitis], gastrointestinal toxicities, hepatic toxicity, infection, neutropenia, thrombocytopenia, anemia, rash/cutaneous skin reactions, and nausea/vomiting), including dose modification, are provided in Appendix 15. Approved prescribing information for other drugs used to treat relapsed or refractory lymphoma should be utilized to guide management of toxicities associated with these drugs.

5.5 Concomitant Therapy and Food

5.5.1 Permitted Therapy

Concomitant therapy includes any medication (eg, prescription drugs, over the counter drugs, homeopathic remedies, or 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 the electronic case report form (eCRF).

5.5.2 Prohibited Therapy and Food

CYP3A is one of the CYP enzymes involved in the metabolism of HMPL-523, but the extent of its involvement is unclear. There is no clinical data on the effect of CYP3A inhibitor or inducer on HMPL-523 PK at this time. Therefore, strong inhibitors or inducers of CYP3A are prohibited throughout the study.

In vitro data suggested that HMPL-523 has the potential to induce CYP3A, CYP1A2, and CYP2B6. Substrates of CYP3A4, CYP2B6, or CYP1A2 that are identified as narrow therapeutic drugs are prohibited during the study; CYP3A4/5, CYP2B6, and CYP1A2 sensitive substrates should be used with caution.

In vitro data suggested that HMPL-523 CCI has the potential to inhibit P-gp, BCRP, and MATE1/2-K, but the clinical relevance is unknown at this moment. Based on these findings, concomitant medications that are sensitive substrates of P-gp, BCRP, or MATE1/2-K identified as narrow therapeutic window drugs should be avoided during the study 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 DDIs.

Lists of prohibited drugs and those that should be used with caution are provided in Appendix 7. These lists are not intended to be exhaustive; please refer to the full prescribing information for all drugs prior to concomitant use with HMPL-523.

Concomitant medications that are known to prolong the QT interval should be avoided (Appendix 16). If the use of any of these drugs is necessary, the risks and benefits should be discussed with the medical monitor prior to its concomitant use with HMPL-523.

The patients shall not receive other antitumor therapies or procedures concomitantly throughout the study, including chemotherapy, radiotherapy, biologic therapy, stem cell transplantation, or other investigational drug therapies for study disease.

Herbal medicines with antitumor effects shall not be used during the study. Patients who take any of these products will be considered to have experienced treatment failure, and treatment with HMPL-523 will be discontinued.

If a patient needs to undergo palliative local radiotherapy to relieve disease-related symptoms (such as local radiotherapy to relieve cancer bone pain), the patient may resume administration of the study investigational drug 7 days after the local radiotherapy is over but should meet the following conditions:

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

If a patient requires localized surgery for palliative purposes to relieve disease -related symptoms or to treat second primary tumors, the following may be considered after discussion with the sponsor to ensure that the surgical procedure does not involve target lesions. This would also require planning for a sufficient hold of investigational drug before and after the surgery to ensure adequate wound healing:

- Stopping HMPL-523 at least 1 week prior to surgery.
- In the case of a major surgery, holding HMPL-523 at least 2 weeks post-surgery to ensure proper wound healing and no other surgery-related AEs are ongoing.
- Evaluating primary lymphoma/CLL to ensure there is no disease progression during the treatment hold.
- Ensuring no other prohibited concomitant therapy is planned.

No grapefruit or grapefruit juice (except small amounts as described in Appendix 7), excessive alcohol, or any recreational drugs will be allowed during the study.

HMPL-523 shows pH-dependent solubility (ie, solubility at pH 6.8 < solubility at pH 1 to 2) and may be less well absorbed as the gastrointestinal pH increases. Subjects should avoid concomitant use of acid-reducing agents during treatment with HMPL-523. If concomitant use of an acid-reducing agent is unavoidable, H_2-antagonist (eg, famotidine, ranitidine, and nizatidine) may be used but should be administered approximately 10 hours before or 2 hours after HMPL-523 dosing. Antacid may be used, but the antacid dose should be administered at least 2 hours before or 2 hours after HMPL-523 dosing. Proton pump inhibitors (eg, esomeprazole, lansoprazole, and pantoprazole) should be avoided during the study. If the investigator believes it is necessary for the patient to use proton pump inhibitor, consent of the sponsor-appointed medical monitor should be obtained before use, and close observation should be performed

during use for a possible reduction in efficacy due to drug interactions. The dose regimen start date and end date of proton pump inhibitor should be recorded.

5.6 Study Assessments

5.6.1 Definitions of Study Assessments

All patients will be closely monitored for safety and tolerability throughout the study. Continuous dosing with HMPL-523 will be offered to patients 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.

The schedule of assessments is provided in Appendix 1, and the schedule of PK sample collection is provided in Appendix 2 and Appendix 3. Unless otherwise indicated, the visit window during the treatment period is ± 3 days (± 1 day during the DLT observation window). Except for the electrocardiogram (ECG), echocardiogram/multigated acquisition scan (MUGA), bone marrow biopsy, and/or aspirate and tumor assessment, all the assessments should be performed before dosing if the study drug is to be taken on the visit day. Unscheduled assessments can be performed if there is a clinical indication.

5.6.2 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the study participant before any study specific screening tests or evaluations using an ICF approved by the local Institutional Review Board/Independent Ethics Committee (IRB/IEC) that contains all elements required by ICH E6(R2) and in compliance with country specific regulation and guidelines before any study-specific screening tests or evaluations are performed. 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.

If a subject cannot sign the ICF (eg, due to an inability to read or write), a legally acceptable representative of the subject must sign the ICF. If both the subject and the legally acceptable representative are not able to read and write, an impartial witness should be present throughout the whole process of providing informed consent. Once the subject and the legally acceptable representative give their oral consent, the ICF should be signed by the impartial witness to confirm that the subject and the legally acceptable representative fully understand the study and their right to withdraw informed consent without any limitations.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before Cycle 1 Day 1. Screening tests will be performed within 21 days preceding the day of the first dose of the study drug, unless otherwise specified. Results of standard of care tests performed before the patient has provided written informed consent and within 21 days preceding the day of the first dose of the study drug may be used; such tests do not need to be repeated for screening. The investigator will maintain a screening log to record details of all patients screened and the reasons for screening failures. Eligibility verification forms will be maintained by investigator and confirmed with sponsor before Cycle 1 Day 1.

5.6.3 Medical History and Demographic Data

Medical history and demographic data will be collected at screening. Medical history includes clinically significant diseases or symptoms; 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, and night sweats for more than 1 month without evidence of infection]); prior cancer diagnosis (including tumor type, initial diagnosis date, immunohistochemistry [IHC], flow cytometry, other pathological findings); prior anticancer therapies, procedures, and related outcomes; and use of tobacco, alcohol, and drugs of abuse prior to the screening visit.

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

5.6.4 Concomitant Medication/Concomitant Procedure

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

5.6.5 Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix 8) should be assessed by the same study personnel at screening, Days 1 and 15 of Cycle 1, Days 1 and 15 of Cycle 2, Day 1 of every cycle from Cycle 3 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.

5.6.6 Rai/Binet Staging, Ann Arbor Staging, and International Prognostic Index

Appendix 9 and Appendix 10 provide a description of Rai and Binet staging, respectively, for patients with CLL.

Appendix 11 provides a description of Ann Arbor staging for patients with lymphoma other than CLL.

Appendix 12 provides information on the different International Prognostic Index (IPI) for patients with FL, MCL, WM/LPL, and other lymphomas.

Rai/Binet staging, Ann Arbor staging, and IPI score will be collected at screening.

Prognostic factors of CLL, including cytogenetic testing result (eg, chromosome 17p del) and immunoglobulin heavy-chain variable (IGHV) mutation status, should be collected at screening if available.

5.6.7 Vital Signs

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

5.6.8 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, height, and weight. Physical examination should be performed at screening; Days 1, 8, 15, and 22 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every cycle from Cycle 3 onwards; and at study completion or early termination. 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.

5.6.9 Laboratory Assessments

Samples for hematology, chemistry panel, fasting lipid profile, serum amylase and lipase, coagulation, viral serology, urinalysis, pregnancy testing, and leukocyte immunophenotyping will be analyzed at the study site's local laboratory. Laboratory assessments will include the following:

- Hematology consists of complete blood count, including red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. Hematology should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine); Days 8, 15, and 22 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every cycle from Cycle 3 onwards; and at study completion or early termination.
- The chemistry panel includes blood urea nitrogen or urea, sodium, potassium, magnesium, chloride, calcium, phosphorus, fasting glucose, ALT, total and direct bilirubin, AST, ALP, lactate dehydrogenase (LDH), uric acid, protein (total), albumin, creatinine, and estimated CrCl (per Cockcroft-Gault). Chemistry should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine); Days 8, 15, and 22 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every cycle from Cycle 3 onwards; and at study completion or early termination.
- Serum beta 2-microglobulin (β2M) should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine), Day 1 of every cycle from Cycle 2 onwards and at study completion or early termination.
- Fasting lipid profile includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. It should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine), Day 1 of every cycle from Cycle 2 onwards, and at study completion or early termination.
- Serum amylase and lipase should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine); Days 8, 15, and 22 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every cycle from Cycle 3 onwards; and at study completion or early termination.
- Coagulation (INR, aPTT, and PT) should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine), Day 1 of every cycle from Cycle 2 onwards, and at study completion or early termination.
- Viral serology should be tested at screening and include the following:

  - HIV
  - HBV (HBsAg and HBcAb; also HBsAb 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 antibody; also, CMV DNA by PCR if the patient is CMV antibody positive)

- Urinalysis or dipstick (pH, specific gravity, glucose, protein, ketones, and blood), should be tested at screening (preferably within 7 days prior to the first dose of the investigational medicine); Day 15 of Cycle 1; Days 1 and 15 of Cycle 2; Day 1 of every cycle from Cycle 3 onwards; and at study completion or early termination. If protein ≥ 2+ during the period of study treatment, a 24-hour urine test should be conducted within 1 week.
- Leukocyte immunophenotyping (fluorescence-activated cell sorting subsets) should be done at screening (preferably within 7 days prior to the first dose of the investigational medicine), Day 15 of Cycle 1, and Day 1 of Cycle 2, which includes:

  - Determination of T lymphocyte/B lymphocyte/natural killer cell counts (CD3, CD19, CD4, CD8, and CD16/56) using a standard cell marker panel.
  - Patients with CLL: 17p del/TP53 mutation status at screening (optional).

  As of Amendment 5, leukocyte immunophenotyping will not be performed from Cycle 3 onwards.

- All women who are not postmenopausal (no menses for at least 1 year without alternative medical cause) will have a serum β-HCG test at screening and study completion or early termination.
- WM/LPL related testing:

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

5.6.10 Electrocardiogram

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

Triplicate ECGs, approximately 2 minutes apart, should be performed at screening and pre-dose and at 4 hours ± 15 minutes post dose on Days 1 and 15 of Cycle 1 in order to evaluate concentration-QT relationship for HMPL-523. Single ECGs will be conducted at any time on Day 1 of Cycle 2. From Cycle 3 onwards, ECGs will be performed as clinically indicated.

Electrocardiograms will be reviewed by the investigator to determine patient eligibility at screening. Additional ECGs and other cardiac monitoring will be provided as clinically indicated during the study.

5.6.11 Echocardiogram/Multigated Acquisition Scan

An echocardiogram/MUGA to assess left ventricular ejection fraction will be conducted at screening and at study completion or early termination.

5.6.12 Tumor and Response Evaluation

All evaluable lesions should be assessed and documented at screening and re-assessed at each subsequent tumor evaluation, using blood test, physical examination, and contrast-enhanced CT scans (neck, chest, abdomen, and pelvis) for indolent NHL and/or positron emission tomography (PET)-CT for HL and aggressive NHL. Enhanced magnetic resonance imaging (MRI) may be used instead of enhanced 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 until the patient has the first progression, starts new anticancer therapy, or dies. Patients who discontinue study drug due to reasons other than disease progression will remain on the study and will be followed quarterly for tumor assessment until the patient has their first progression, starts new anticancer therapy, or dies or until 12 months after their initial dose of the study drug. Tumor assessment will also be conducted at study completion or early termination (for reasons other than disease progression).

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

5.6.13 Bone Marrow Aspirate and/or Biopsy

A bone marrow biopsy and/or aspirate is strongly recommended to be done at screening or up to 3 months before the Cycle 1 Day 1 and for confirmatory purposes when the patient is considered to be likely CR with enhanced CT and other assessments or to confirm suspected PD based solely upon declines in the platelet count and/or hemoglobin.

5.7 Participant Completion/Discontinuation

5.7.1 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-523 administration for a follow-up visit. Ongoing TEAEs thought to be related to HMPL-523 will be followed until the event has resolved to baseline grade, the event is assessed as stable by the investigator, new antitumor treatment is initiated, the patient is lost to follow-up, the patient withdraws from the study, or it has been determined that the study treatment or participation is not the cause of the AE, whichever comes first.

Follow-up (Extended Monitoring)

Patients who discontinue the study drug due to reasons other than disease progression will remain on the study and will be followed quarterly for tumor assessment until the patient has the first progression, starts new anticancer therapy, dies, or until 12 months after the initial dose with the study drug. The assessments to be performed at the follow-up visits are listed in the Schedule of Activities in Appendix 1.

5.7.2 Participant 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
- Noncompliance (eg, frequently misses doses, visits)

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

5.7.3 Study Treatment Discontinuation

Patient must discontinue the study treatment in case of:

- Disease progression
- Intolerable toxicity
- Use of other antitumor therapy as described in Section 5.5.2
- Pregnancy with onset during study

The primary reason for study treatment discontinuation should be recorded on the appropriate CRF. Discontinuation from HMPL-523 treatment does not mean discontinuation from the study, and the remaining study procedures should be completed as indicated in the study protocol.

5.8 Study/Site Discontinuation and Closure

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 principal investigator will promptly inform study participants and the IRB/IEC. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule. Reasons for suspension or termination of the study may include the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- 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
- Sponsor decision to discontinue clinical development of the drug in the specific indication or in the specific region

If the study was suspended for safety or quality issues, 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. For instance, the study must comply with the European Medicines Agency guideline, 'Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.'

5.9 Pharmacokinetic and Pharmacodynamic Assessments

5.9.1 Collection Schedule

Blood samples will be collected at scheduled time points specified in Appendix 2 for the dose escalation stage and in Appendix 3 for the dose expansion stage. Upon implementation of Protocol Amendment 5, PK samples for measurement of plasma concentrations of HMPL-523 CCI will not be collected on Cycle 5 Day 1 and beyond in the dose expansion phase.

Additional PK samples are allowed to be collected for patients who experience a clinically significant safety event to facilitate the understanding of the relationship between the safety event and the exposure of the investigational drug. These additional samples may be obtained as agreed upon by the investigator and the sponsor's medical monitor.

After each venous blood sampling, the exact time and dates of blood sampling will be recorded in the patient's source documentation such as eCRF.

Blood samples that remain after PK analysis of HMPL-523 in the dose escalation stage or pharmacodynamic samples collected fresh in the dose expansion stage may be used exclusively for exploratory purposes. These may include pharmacodynamics biomarker study such as to detect the changes of expression level of chemokines (CCL22, CXCL13, CCL3, etc) in plasma after HMPL-523 treatment. Pharmacokinetic and pharmacodynamic biomarker correlations will be analyzed.

Tumor biopsies will be collected during the screening period for all patients in the dose expansion cohorts for the evaluation of candidate biomarkers including, but not limited to, biomarkers within tumor and/or within periphery as predictive biomarkers of efficacy of HMPL-523 (refer to Appendix 1). If it is not feasible to collect fresh biopsy or archival tissue, the sponsor may waive biopsy requirement in selected patients. For archival tissue, cell block or 10 unstained slides should be submitted. For CLL patients or patients with bone marrow involvement, bone marrow biopsy can be submitted to fulfill the biopsy requirement.

Samples remaining after the predefined analysis is complete may be held for future biomarker analysis.

5.9.2 Samples Handling and Shipment

Pharmacokinetic and pharmacodynamic sample processing, storage, and shipment instructions will be detailed in the laboratory manual.

5.9.3 Analytical Procedures

Plasma samples will be analyzed to determine the concentrations of HMPL-523 CCI using a validated Liquid Chromatography-Tandem Mass Spectrometry method. If required, the plasma samples may be analyzed to document the presence of CCI using a qualified research method.

Chemokines (CCL22, CXCL13, CCL3, etc.) levels in plasma samples will be determined using a multiplex array.

6 ASSESSMENT OF SAFETY

6.1 Safety Plan

Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of TEAEs, physical examinations, and laboratory measurements.

No evidence available at the time of the release of this protocol indicates that special warnings or precautions are appropriate, other than those will be noted in the HMPL-523 IB.

6.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording 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 study drug.

The sponsor or the 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

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can 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 those described in Section 6.4.8
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from the study drug
- Related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies)

6.2.2 Serious Adverse Events

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

- Fatal (ie, the AE actually causes or leads to death, except for deaths caused by the progress of the disease)
- Life threatening (ie, the AE, in the view of the investigator, places the patient at immediate risk of death; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization (excluding emergency or outpatient treatment)

- Results in persistent or significant disability/incapacity (ie, 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 investigational product(s)
- Considered a significant medical event by the investigator (eg, 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 nonserious 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.

SAEs are required to be reported by the investigator to the sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 6.5.1 for reporting instructions and Section 6.3.1 for AE reporting period).

All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Depending on the event, follow-up may require additional tests or medical procedures as indicated and/or referral to a general physician or a medical specialist. All pregnancies that occur during participation in the study should be followed to determine the outcome of the pregnancy.

6.2.3 Protocol-Defined Events of Special Interest Expedited Adverse Events

Nonserious AEs of special interest are required to be reported by the investigator to the sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 6.5.1 for reporting instructions). AEs of special interest for this study include the following:

- Hepatotoxicity, including cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 6.4.5 and Appendix 13)
- Infective pneumonia
- Interstitial lung disease/Pneumonitis
- Kidney injury

6.2.4 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 learning of the event. Investigators will also participate in regular teleconference SRC meetings with the medical monitor and the sponsor, during which they will report any DLTs observed during the DLT assessment window for each patient in the dose-escalation stage of the study. The SRC recommendation form will be completed and signed after the dose escalation meeting by the chairperson of the SRC.

6.3 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 patient's source documentations and CRF and reported to the sponsor or the sponsor's designee in accordance with protocol instructions.

6.3.1 Adverse Event Reporting Period

After informed consent has been obtained, all SAEs regardless of attribution will be collected until 30 days after the last administration of study treatment or study discontinuation/termination, whichever is later.

After initiation of study medications, all AEs regardless of attribution will be collected until 30 days after the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, the investigators should report only SAEs that are related to prior HMPL-523 treatment (see Section 6.7).

6.3.2 Eliciting Adverse Events

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

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

6.3.3 Assessment of Severity and Causality of Adverse Events

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 source documentation and CRF, the investigator will make an assessment of seriousness (see Section 6.2.2 for seriousness criteria), severity, and causality.

Table 4 provides guidance for grading AE severity, and Table 5 provides guidance for assessing the causal relationship to the investigational product.

AE grading should be in accordance with NCI CTCAE v5.0. For AE terms that cannot be found in CTCAE v5.0, general guidelines for 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 study drug. To ensure consistency of causality assessments, investigators should apply the general guidelines provided in Table 5.

Table 4 AEs Grading (Severity) Scale

Grade	Severity	Alternate Description[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	

Abbreviations: ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; SAE = serious adverse event.
Note: NCI CTCAE v5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Note: Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to definition of a SAE (see Section 6.2.2).
[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events 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 refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 5 Causality Attribution Guidance

Causality	Guidance
Related	An AE will be considered "related" to the use of the investigational drug if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to, a positive rechallenge, 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 AE, or a lack of an alternative explanation for the AE.
Not Related	An AE event will be considered "not related" to the use of the investigational drug 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 AE, or the presence of a more likely alternative explanation for the AE.

AE = adverse event.

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 the investigator decides that the SAE is not related to the study drug, the investigator must provide another cause of event for the SAE. If the investigator decides that the SAE is related to the study drug, the investigator should provide the rationale of causality to the study medication.

6.4 Procedures for Recording Adverse Events

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

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

Only 1 AE term should be recorded in each event field on the CRF.

6.4.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (eg, 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.

6.4.2 Adverse Events Occurring Secondary to Other Events

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

6.4.3 Persistent or Recurrent Adverse Events

A persistent AE extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an AE/SAE CRF.

A recurrent AE occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an AE/SAE CRF, respectively.

6.4.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (eg, abnormalities that require study drug 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 (eg, ALP and bilirubin 5× ULN associated with cholecystitis), only the diagnosis (eg, 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.

6.4.5 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). Therefore, investigators must report an AE of special interest upon the occurrence of either of the following:

- Treatment-emergent ALT or AST ≥ 3 × ULN in combination with total bilirubin > 2 × ULN
- 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 AE CRF (see Section 6.4.1) and reported to the sponsor's designee as a nonserious AE of special interest (see Section 6.5.1).

6.4.6 Deaths

For this study, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 6.3.1) that are attributed by the investigator solely to progression of hematological malignancy under current investigation should be recorded only on the Study Completion/Early Discontinuation CRF. All other on-study deaths, regardless of their relationship to the study drug, must be recorded on the AE CRF and immediately reported to the sponsor (see Section 6.5.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE CRF. Generally, only 1 such event should be reported. 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 pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE CRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

6.4.7 Preexisting Medical Conditions

A preexisting medical condition 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 pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

6.4.8 Worsening of Hematologic Malignancy

Worsening and/or progression of the hematologic malignancy (eg, leukemia or lymphoma) should not be recorded as an AE or SAE, unless the progression directly leads to the patient's death, in which case the disease progression should be reported as a CTCAE Grade 5 SAE. All worsening and/or progression of the hematologic malignancy data will be captured as efficacy assessment data.

Hospitalization due solely to the progression of underlying lymphoma should not be reported as an SAE. 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, or 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.

6.4.9 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 pre-existing 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 an SAE (Section 6.2.2).

All hospitalizations (including any overnight stay in an acute care hospital) should also be documented on the medical source document with the admission and discharge dates.

6.4.10 Pregnancy

If a female patient becomes pregnant while receiving the study drug or within 30 days after the last dose of investigational product, a pregnancy report should be reported within 24 hours of

learning of the pregnancy to the sponsor's drug safety department or the sponsor's designee. Pregnancy should be recorded on the pregnancy CRF but not the AE CRF.

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

Spontaneous abortion should always be classified as an SAE (as the sponsor considers these medically significant), recorded on an AE CRF, and expeditiously reported to the sponsor or the sponsor's designee (see Section 6.5.1).

Any congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug should be classified as an SAE, recorded on the AE CRF, and expeditiously reported to the sponsor or the sponsor's designee (see Section 6.5.1).

After the study period, abortions, congenital anomalies/birth defects, and pregnancy outcomes should still be reported expeditiously to the sponsor or the sponsor's designee.

6.5 Expedited Reporting From Investigator to Sponsor

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 the study drug:

- SAEs (see Section 6.5.1 for further details)
- Nonserious AEs of special interest (see Section 6.5.1 for further details)
- Pregnancies

6.5.1 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 the sponsor or the sponsor's designee via fax or email within 24 hours of learning of the events.

For initial SAEs 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 the sponsor or the sponsor's designee as soon as it becomes available and/or upon request within 24 hours of the investigator's awareness of the events.

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

6.5.2 Regulatory Reporting Requirements for Serious Adverse Events

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

The 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. The 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 a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.6 Type and Duration of Follow-up of Patients After Adverse Events

The investigator should follow up all unresolved AEs (including SAEs and DLTs) until the event resolves to baseline grade, the event is assessed by the investigator as stable, new antitumor treatment is initiated, the patient is lost to follow-up, the patient withdraws from the study, or 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 AE 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 their outcome.

For some SAEs, the sponsor or the sponsor's designee may follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (eg, 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 HMPL-523 treatment.

The investigator should notify the sponsor or the sponsor's designee of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if it is felt to be related to prior HMPL-523 treatment. The investigator is not obligated to actively monitor patients for AEs once the trial has ended. The sponsor or the sponsor's designee should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

7 STATISTICAL ANALYSIS

7.1 Determination of Sample Size

The study is closed to new enrollment; the last patient was enrolled on CCI [redacted]. The total number of patients enrolled in the dose-expansion phase of the study at the time of enrollment closure is 48, with 3 patients continuing on treatment.

The sample size rationale for the study prior to closing for further enrollment is described below.

7.1.1 Stage 1: Dose Escalation

The sample size for Stage 1 is based on the dose-escalation rules of the 3 + 3 design. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 such AE in a given cohort of 6 patients is 46.9%, 26.5%, and 5.8%, respectively.

7.1.2 Stage 2: Dose Expansion

The planned enrollment for Stage 2 was approximately 70 patients. A total of 70 patients will provide more robust safety data in the patient populations studied. For a given AE with a true rate of 10%, 5%, or 1%, the probability of observing at least 1 such AE in 70 patients is 99.9%, 97.2%, and 50.5%, respectively.

7.2 Analysis Population

The following analysis populations are defined for the study:

Full Analysis Set (FAS):

The FAS is defined as all patients who receive at least 1 dose of HMPL-523. The FAS will be used for analysis of safety data and efficacy data.

DLT Evaluable Analysis Set:

The DLT Evaluable Analysis Set is defined as 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

Response Evaluable Set (RES):

The RES is defined as all patients who receive at least 1 dose of HMPL-523, have either a baseline tumor measurement for patients with non-WM/LPL or baseline quantitative serum immunoglobulin assessment for patients with WM/LPL, and have at least 1 post-baseline tumor measurement or clinical restaging. The RES will be the primary population for the analysis of ORR, TTR, and DoR.

Pharmacokinetics Analysis Set (PKAS):

The PKAS is defined as all patients who received at least 1 dose of HMPL-523 and have at least 1 PK sample obtained and analyzed.

7.3 Analysis Planned

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 finalized prior to database lock.

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.

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 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, gender, race, ethnicity, weight, height, type of malignancy, duration of malignancy, site of disease involved, and baseline ECOG performance status, will be summarized descriptively for the FAS. All summaries will be presented for each dose level in stage 1 and type of malignancy in stage 2.

7.3.2 Disposition of Patients Enrolled in the Study

The disposition of patients enrolled in the dose escalation and dose expansion stages will be summarized.

Study drug administration data will be listed by dose level and type of malignancy. The total duration of exposure, dose intensity, and relative dose intensity of HMPL-523 will be summarized by descriptive statistics.

7.3.3 Safety Analysis

Safety parameters, including DLTs, recorded TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG parameters, and physical examination findings, will be summarized by dose level in the dose escalation stage and by type of malignancy in the dose expansion stage for the FAS.

7.3.3.1 Dose-Limiting Toxicities

All DLTs will be listed.

7.3.3.2 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 v5.0.

Summaries will be presented for TEAEs. An AE is considered a TEAE if the onset date is on or after the start of study treatment or if the onset date is missing, or if the AE has an onset date before the start of study treatment but worsened in severity after the study treatment until 37 days after the last dose of study treatment. All TEAEs will be listed and the frequency of patients reporting TEAEs will be summarized by MedDRA System Organ Class and Preferred Term and NCI CTCAE grade.

The same analysis will be performed for SAEs; causality-related TEAEs assessed by the investigators; AEs leading to dose interruption, reduction, or treatment discontinuation; and protocol-defined AEs of special interest.

7.3.3.3 Clinical Laboratory Test Values

Descriptive statistics for each clinical laboratory test will be presented for each dose level and scheduled visit in the dose escalation stage and also by type of malignancy in the dose expansion stage. Laboratory test values from the hematology and chemistry panels, which can be graded by NCI CTCAE, will be summarized by the shift of NCI CTCAE grade from baseline to the highest grade reported during the study.

Selected laboratory tests may be plotted over time for each patient.

All laboratory test results will be listed.

7.3.3.4 Vital Signs

Descriptive statistics for systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature will be summarized by dose level and type of malignancy by scheduled visit.

Selected vital signs tests may be plotted over time for each patient.

All vital sign data will be listed.

7.3.3.5 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 type of malignancy by visit.

7.3.3.6 Physical Examination

All physical examination findings will be listed.

7.3.4 Pharmacokinetic Analysis

PK parameters will be analyzed with the PKAS. A noncompartmental model analysis will be performed for plasma concentration data by a central laboratory using Phoenix WinNonlin. Individual and mean plasma concentration of HMPL-523 CCI versus time data will be tabulated and presented. The individual and mean PK parameters determined following analysis of the concentration of HMPL-523 and CCI versus time data will include, but

not be limited to, plasma exposure (AUC_{0-t} and AUC_{tau}), C_{max}, T_{max}, C_{min}, CL/F, AR, and MP ratio. N, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation will be presented. The actual times of plasma sample collection will be used in the determination of the PK parameters. Details of PK analysis, including data handling rules and software used to perform PK analysis, will be provided in the statistical or PK analysis plan.

Individual and mean HMPL-523 and CCI concentrations will be plotted by dose level.

7.3.5 Efficacy Analysis

Efficacy analysis will be performed for the RES for ORR, TTR, and DoR endpoints and the FAS for the PFS endpoint. Efficacy endpoints will be summarized by dose level in the dose escalation stage and by type of malignancy (when feasible) in the dose expansion stage.

The estimated ORR and 95% confidence interval based on the Clopper-Pearson method will be presented.

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

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

Tumor assessment in different subgroups will be evaluated according to specified guidelines/criteria:

- Chronic lymphocytic leukemia: the modified International Workshop on CLL guideline (modified IWCLL 2008, see Appendix 4)
- WM/LPL: consensus of international workshops on WM (IWWM-7 Consensus, see Appendix 5)
- Lymphoma other than CLL or WM/LPL: Lugano Response Criteria for Hodgkin and NHL (Cheson et al 2014, see Appendix 6)

7.3.6 Biomarker Analysis

Levels of chemokines in plasma will be tabulated and summarized using descriptive statistics as appropriate. Correlation between drug exposure level of HMPL-523 in plasma and chemokines level and biomarker changes in plasma in all subtypes or different subtypes of lymphoma will be analyzed using descriptive and graphical means. Exploratory data will not be included in the clinical study report, and a separate summary will be prepared.

7.4 Interim Analysis (Not Applicable)

There is no interim analysis in this study.

8 ETHICS

8.1 Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and any 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 the 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 the sponsor's designee, investigators are required to promptly report to their respective IRB/IEC 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, ICH E6(R2) guidelines, Clinical Trials Regulation (EU 536/2014), the 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 Good Clinical Practice (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 ICF 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 ICF 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 ICFs, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study. Signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

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.

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 Protections 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 are 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 ICF (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 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.

Appendix 17 describes the measures that HUTCHMED Limited has put in place to meet the requirements of the data protection laws for EU member states.

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 (ie, 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. They 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, X-rays, 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 (ie, 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 (eg, 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

The study should be recorded accurately by investigators so that study data can be verified. The study documents can be divided into 2 types: investigator documents and subject source data. Investigator documents include the protocol and amendments, the eCRF and data clarification forms, approvals, correspondence with the IRB and regulatory authorities, ICF, HMPL-523 records, study personnel curriculum vitae, authorization forms, and any other essential documents.

Subject source data documents (recording primary efficacy/safety data) include study site/hospital medical history, scheduled visit dates, original laboratory test results, ECGs,

electroencephalograms, radiological imaging, pathological and specific assessment reports, signed ICF(s), medical records, and subject screening forms. The documents mentioned above should be properly stored by the investigator for 25 years after the study is completed or longer if mandated by local regulatory requirements. Subject medical files will be archived in accordance with national law. If investigators need to transfer the documents to another party or place, the Sponsor must be notified in advance. It is the responsibility of the Sponsor to inform the investigator as to when these documents no longer need to be retained.

The Sponsor will store the study documentation for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of HMPL-523; or until at least 25 years after the end of the study, whichever is longer.

If the documents cannot be stored properly at the study site, the documents may be transferred by the investigator and Sponsor to an approved storage facility. The documents must be sealed for storage and easily found for review in the case of a regulatory authority audit. If the documents are still in use, they can be made available as certified copies and stored elsewhere. For remote visits utilizing Study Hub, study data will be retained in Study Hub until the end of the study.

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 HUTCHMED Limited's designee to check study data, patients' medical records, and CRFs. The principal investigator will permit monitor/sponsor's representatives and collaborators from 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 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 monitor must verify that the patient received the study drug assigned by the dose level. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The investigator (or deputy) agrees to cooperate with the 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 designee standard operation procedures. Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor (SDV) and the maintenance of a drug-dispensing log by the investigator. A CRO will be responsible for the data management of this study, including quality checking of the data. Sites will be responsible for data entry into the electronic data capture (EDC) system. In the event of discrepant data, the CRO will request data clarification from the sites.

The sponsor will perform oversight of the data management of this study.

11.2 Electronic Case Report Forms

Electronic data capture will be used for this study, meaning that all eCRF 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.

All data must be entered in English. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF 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. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, and the time and date of the change will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the investigator. This will be audit trailed by the EDC application meaning that the name of the investigational staff and the time and date stamps are captured.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each patient who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, 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.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique user identification (ID). Specified records will be electronically signed by

the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique user ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF 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 (eg, on a compact disc). Data must be kept with the study records.

11.3 Coding

AEs will be coded using MedDRA. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

12 USE OF INFORMATION AND PUBLICATION

12.1 Use of Information

All information regarding HMPL-523 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-523. 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 the International Committee of Medical Journal Editors authorship requirements at 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.

Irrespective of the outcome of the study, the Sponsor will submit a summary of the results of the clinical study to any relevant database within 1 year from the end of the global clinical study. It will be accompanied by a summary written in a manner that is understandable to laypersons.

For studies conducted under Regulation (EU 536/2014) where the study has ended in all member states concerned in the EU/European Economic Area but is still ongoing in other regions and data from those regions are not available (making the statistical analysis not relevant), the summary of results must be submitted to the EU database as soon as it is available but no later than 1 year after the end of the study globally.

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 the sponsor's personnel exceeds 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 with 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's confidential information in any such paper and agree 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-523 and, therefore, may be disclosed as required to other clinical investigators, other pharmaceutical companies, or 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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14 APPENDICES

APPENDIX 1 SCHEDULE OF ACTIVITIES

Procedures / Study Day	Screening		Treatment[2]							Follow-up[3]	
			Cycle 1				Cycle 2		Cycle 3 and Onwards		
	D-21 to D-1	D-7 to D-1	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±3)	D1 (±3)	Study Completion or Early Termination (30±7 Days After the End of Treatment)	Follow-up on Day 1 (±7) Quarterly After the End of Treatment
Informed consent[1]	X										
Demographics[4]	X										
Medical history[5]	X										
Height	X										
Physical examination[6]	X		X	X	X	X	X	X	X	X	
ECOG performance status	X		X		X		X	X	X	X	
Vital signs[7]	X		X	X	X	X	X	X	X	X	
Concomitant medication/procedure[8]	X		X	X	X	X	X	X	X	X	
Hematology[9]		X		X	X	X	X	X	X	X	
Urinalysis/dipstick[10, 24]		X			X		X	X	X	X	
Chemistry panel[11, 24]		X		X	X	X	X	X	X	X	
Beta 2-microglobulin[24]		X					X		X	X	
Fasting lipid profile[12,24]		X					X		X	X	
Serum amylase and lipase[24]		X		X	X	X	X	X	X	X	
Coagulation assay (INR, aPTT, PT) [24]		X					X		X	X	
17p del/TP53 mutation[13,24]	X										
Leukocyte immunophenotyping[14,24]	X				X		X				

Procedures / Study Day	Screening		Treatment[2]							Follow-up[3]	
			Cycle 1				Cycle 2		Cycle 3 and Onwards		
	D-21 to D-1	D-7 to D-1	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±3)	D1 (±3)	Study Completion or Early Termination (30±7 Days After the End of Treatment)	Follow-up on Day 1 (±7) Quarterly After the End of Treatment
HIV, HBV, HCV, and CMV screening[15]	X										
Pregnancy tests[16]	X									X	
Bone marrow examination (biopsy and/or aspirate)[17]	X										
Tumor biopsy[25]	X										
Echocardiogram/MUGA	X									X	
12-Lead ECG[18]	X		X		X		X		As clinically needed	X	
Arbor staging, IPI score, and Rai and/or Binet staging	X										
Quantitative serum immunoglobulin levels (for WM/LPL)[19,24]	X						X		X	X	X
CT/PET-CT[20]	X								X	X	X
Tumor assessment[21]	X								X	X	X
PK and Pharmacodynamics plasma sampling[22]			Refer to Appendix 2 and Appendix 3								
Plasma collection for exploratory biomarkers[22]			X		X		X				
AE[23]	X		X	X	X	X	X	X	X	X	
HMPL-523 treatment			X								
Psychological evaluation	X										

β-HCG = beta human chorionic gonadotropin; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR = complete response; CrCl = creatinine clearance; CT = computed tomography; D = day; DLT = dose-limiting toxicity; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HL = Hodgkin's lymphoma; IgA = Immunoglobulin A; IgG = Immunoglobulin G; IgM = immunoglobulin M; IHC = immunohistochemistry; INR = international normalized ratio; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LPL = lymphoplasmacytic lymphoma; MUGA = multigated acquisition scan; NHL = non-Hodgkin's lymphoma; PCR = polymerase chain reaction; PD = progressive disease; PET = positron-emission tomography; PK = pharmacokinetic; PR = partial response; PT = prothrombin time; QTcF = corrected QT interval with Fridericia; RNA = ribonucleic acid; SAE = serious adverse event; WM = Waldenström's macroglobulinemia.

1 Informed consent must be documented before any study-specific screening procedure is performed.

2 Unless otherwise indicated, the visit window during the treatment period will be ±3 days (±1 day during the DLT assessment window). Except for the ECG, echocardiogram/MUGA, bone marrow biopsy, and/or aspirate and tumor assessment, all the assessments should be performed before dosing if the study drug is to be taken on the visit day. Unscheduled assessments could be performed if there is a clinical indication.

3 Patients who complete or prematurely discontinue the study need to return to the study site for a follow-up within 30±7 days after the last dose of HMPL-523. Patients who discontinue the study drug due to reasons other than disease progression will remain on study and be followed quarterly until the patient has the first progression, starts new anticancer therapy, or dies or until 12 months from the initial dose with the study drug have passed.

4 Demographic data include date of birth, gender, and self-reported race and ethnicity.

5 Medical history includes clinically significant diseases or symptoms, surgeries, cancer history (including constitutional symptoms/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, IHC, flow cytometry, and other pathological findings), prior cancer therapies and procedures), use of tobacco, use of alcohol, and use of drugs of abuse prior to the screening visit.

6 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 and weight. After screening, a change of physical signs from baseline, and newly presented or patient-reported physical signs should be evaluated. Height will be assessed only at screening.

7 Vital signs will include measurements of body temperature (taken under the armpit or in the mouth), heart rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position. The patient should be seated for 5 minutes before the measurement of blood pressure.

8 Concomitant medications include all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to the screening visit and 30 days after the end of treatment. Any concomitant procedure (excluding bone marrow examination) within 7 days prior to the screening visit and 30 days after the end of treatment or early termination should be recorded.

9 Hematology consists of complete blood count, including red blood cell count, hemoglobin, hematocrit, white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

10 Urinalysis or dipstick (pH, specific gravity, glucose, protein, ketones, blood). If protein ≥ 2+ during the period of study treatment, a 24-hour urine test should be conducted within 1 week.

11 The chemistry panel includes blood urea nitrogen or urea, sodium, potassium, magnesium, chloride, calcium, phosphorus, fasting glucose, creatinine and estimated CrCl per Cockcroft-Gault, ALT, bilirubin direct and total, AST, ALP, LDH, uric acid, protein (total), and albumin.

12 Fasting lipid profile includes total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides.

13 17p del/TP53 mutation status is for patients with CLL only and optional.

14 Leukocyte immunophenotyping: T lymphocyte/B lymphocyte/natural killer cell counts (CD3, CD19, CD4, CD8, CD16/56) using a standard cell marker panel, should be tested at baseline and Weeks 3 and 5, every 4 weeks from Weeks 8-24, and then every 12 weeks thereafter until the end of treatment.

[15] HBV: HBsAg and HBcAb; also HBsAb and HBV DNA by PCR if the patient is HBcAb positive; HCV: also HCV RNA by PCR if the patient is HCV antibody positive; CMV: also CMV DNA by PCR if the patient is CMV antibody positive.

[16] All women who are not postmenopausal (≥12 months of nontherapy-induced amenorrhea) will have a serum β-HCG test at screening. In the case of menopausal women, the date of menopause onset should be recorded.

[17] A bone marrow biopsy and/or aspirate is strongly recommended to be done at baseline or up to 3 months before Cycle 1 Day 1 and for confirmatory purposes when the patient is considered to be likely CR with CT assessment and laboratory tests results or to confirm suspected PD based solely upon declines in the platelet count and/or hemoglobin. If a bone marrow examination (biopsy and/or aspirate) has been performed within 3 months of Cycle 1 Day 1, a screening bone marrow examination does not need to be performed unless an investigator feels one is clinically warranted as outlined above. For those patients with initial bone marrow involvement from lymphoma/leukemia at study entry, a repeat biopsy at the end of therapy is necessary to confirm complete clinical response if physical examination and CT scans demonstrate a clinical CR or to confirm suspected PD based solely upon declines in the platelet count and/or hemoglobin. The number of additional/unscheduled bone marrow examinations performed during the study will be at the discretion of the investigator.

[18] A 12-lead ECG should be performed at screening and pre-dose and at 4 hours ± 15 minutes post-dose on Days 1 and 15 in Cycle 1 and at any time on Day 1 of each cycle from Cycle 2 onwards. Triplicate ECGs, approximately 2 minutes apart, will be performed for all patients in baseline and Cycle 1. Additional ECGs and other cardiac monitoring will be provided as clinically indicated during the study. PR interval, QRS interval, RR interval, QT/QTcF interval, and heart rate will be involved in the 12-lead ECG.

[19] Quantitative immunoglobulin assessment of IgM, IgA, and IgG for all patients with WM/LPL. Quantitative immunoglobin assessment should be repeated at the time of the CR confirmation.

[20] Contrast-enhanced CT scans (neck, chest, abdomen, pelvis) should be performed for indolent NHL and/or PET-CT for HL and aggressive NHL.

[21] The baseline tumor assessment can be completed within 21 days prior to enrolment. All measurable and evaluable lesions should be assessed and documented at this visit, using blood, physical examination and CT scan (neck, chest, abdomen, pelvis, liver/spleen) every 8 weeks (±7 days) for the first 24 weeks and then every 12 (±7 days) weeks thereafter. At study termination or early termination (other than disease progression) of the patients, tumor assessment will be also conducted. The same imaging procedure and laboratory tests used to define measurable lesions at baseline should be used throughout the study for each patient.

[22] Blood samples should be collected according to the time-point tables in Appendix 2 and Appendix 3. All patients in the dose expansion stage will be required to provide samples for pharmacodynamics biomarker analysis. Upon implementation of Amendment 5, PK samples for measurement of plasma concentrations of HMPL-523 CCI will not be collected on Cycle 5 Day 1 and beyond in the dose expansion phase.

[23] After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). After initiation of HMPL-523 treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are related to prior HMPL-523 treatment.

[24] Preferably within 7 days prior to the first dose of the study drug.

[25] Fresh or archival tumor tissue consisting of a cell block or 10 unstained slides should be collected for patients in dose expansion cohorts during screening.

APPENDIX 2 PK SAMPLING TIME POINTS (ONCE DAILY) (DOSE ESCALATION STAGE)[d]

Visit Cycle and Day	Time Point
Cycle 1 Day 1	Pre-dose[a]
	30 minutes (±5 minutes) post-dose
	1 hour (±5 minutes) post-dose
	2 hours (±10 minutes) post-dose
	4 hours (±15 minutes) post-dose
	6 hours (±15 minutes) post-dose
	8 hours (±15 minutes) post-dose
Cycle 1 Day 2	Pre-dose[a]
Cycle 1 Day 15	Pre-dose[a]
	30 minutes (±5 minutes) post-dose
	1 hour (±5 minutes) post-dose
	2 hours (±10 minutes) post-dose
	4 hours (±15 minutes) post-dose
	6 hours (±15 minutes) post-dose
	8 hours (±15 minutes) post-dose
Cycle 1 Day 16	Pre-dose[a]
Cycle 1 Day 28[b]	Pre-dose[a]
	30 minutes (±5 minutes) post-dose
	1 hour (±5 minutes) post-dose
	2 hours (±10 minutes) post-dose
	4 hours (±15 minutes) post-dose
	6 hours (±15 minutes) post-dose
	8 hours (±15 minutes) post-dose
Cycle 2 Day 1[c]	Pre-dose[a]

PK = pharmacokinetic.

[a] The blood samples will optimally be obtained within 5 minutes prior to dosing but may be obtained up to 30 minutes prior to dosing.

[b] Cycle 1 Day 28 shares the window with Cycle 2 Day 1, which is ±3 days and should be immediately followed by Cycle 2 Day 1.

[c] Cycle 2 Day 1 pre-dose is the 24-hour (+15 minutes) PK sample of Cycle 1 Day 28.

[d] Blood samples that remain after PK analysis of HMPL-523 may be used exclusively for exploratory biomarker purposes.

APPENDIX 3 PK AND PHARMACODYNAMICS SAMPLING TIME POINTS (DOSE EXPANSION STAGE)[e]

Visit Cycle and Day[f]	Time Point[d]	PK Sample	Pharmacodynamics Sample
Cycle 1 Day 1	Pre-dose[a]	X	X
	30 minutes (±5 minutes) post-dose	X	-
	1 hour (±5 minutes) post-dose	X	-
	2 hours (±10 minutes) post-dose	X	-
	4 hours (±15 minutes) post-dose	X	-
	6 hours (±15 minutes) post-dose	X	-
	8 hours (±15 minutes) post-dose	X	-
Cycle 1 Day 2	Pre-dose[a]	X	-
Cycle 1 Day 28[b, g]	Pre-dose[a]	X	-
	30 minutes (±5 minutes) post-dose	X	-
	1 hour (±5 minutes) post-dose	X	-
	2 hours (±10 minutes) post-dose	X	-
	4 hours (±15 minutes) post-dose	X	-
	6 hours (±15 minutes) post-dose	X	-
	8 hours (±15 minutes) post-dose	X	-
Cycle 2 Day 1[c]	Pre-dose[a]	X	X
Cycle 3 Day 1	Pre-dose[a]	X	X
Cycle 5 Day 1 and every other cycle thereafter[h]	NA	-	

eCRF = electronic case report form; NA = not applicable; PK = pharmacokinetic.

[a] The blood samples will optimally be obtained within 5 minutes prior to dosing but may be obtained up to 30 minutes prior to dosing.

[b] Cycle 1 Day 28 shares the window with Cycle 2 Day 1, which is ±3 days and should be immediately followed by Cycle 2 Day 1.

[c] Cycle 2 Day 1 pre-dose is the 24-hour (+15 mins) PK sample of Cycle 1 Day 28.

[d] The actual date and time of the PK samples must be recorded in the eCRF.

[e] Blood samples that remain after PK analysis of HMPL-523 may be used exclusively for exploratory biomarker purposes.

[f] On PK sampling day, study drug must be taken at the investigative site under the supervision of the investigator or designee and should not be taken at home on the morning of the visits. The date and time of the dose administered on the day of PK collection and 1 day before PK collection must be recorded in the eCRF.

[g] In case PK samples planned for Cycle 1 Day 28 does not occur due to whatever reasons, they may be rescheduled for collection in subsequent cycles. Please consult the sponsor for further guidance and instructions.

[h] Upon implementation of Protocol Amendment 5, PK samples for measurement of plasma concentrations of HMPL-523 will not be collected on Cycle 5 Day 1 and beyond.

APPENDIX 4 INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA UPDATE OF THE NATIONAL CANCER INSTITUTE-WORKING GROUP GUIDELINES: RESPONSE CRITERIA

Complete Response (CR)

Complete response requires all of the following criteria as assessed no earlier than 2 months[a] after completion of therapy:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL)
- Absence of significant lymphadenopathy (nodes ≤15 mm in longest diameter or any extra nodal disease) by physical examination and computed tomography (CT) scan
- No hepatomegaly or splenomegaly by physical examination or CT scan, as appropriate
- Absence of disease or constitutional symptoms (B symptoms).
- Blood counts above the following values:
  - Neutrophils > 1.5×10^9/L (1500/μL) (without growth factors)
  - Platelets > 100×10^9/L (100000/μL) (without platelet transfusion or growth factors)
  - Hemoglobin > 110 g/L (11 g/dL) (without blood transfusions or erythropoietin)
- Bone marrow aspirate and biopsy should be performed 3 months after the last treatment when the clinical and laboratory results listed above demonstrate a CR/cytopenic CR has been achieved. Bone marrow should be at least normocellular for age, with < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. However, this time interval should not exceed 6 months. A marrow biopsy should be compared to a pretreatment marrow if available.

In patients who are otherwise in a complete remission but bone marrow nodules can be identified histologically, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than chronic lymphocytic leukemia (CLL) cells, or CLL cells. Patients with residual CLL cells should be considered to be partial response (PR) (nodular partial response [nPR]).

Complete Response with Incomplete Bone Marrow Recovery

Patients who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia, anemia, thrombocytopenia, or neutropenia. The marrow evaluation described above should be performed with scrutiny and not show any clonal infiltrate.

Partial Response (PR)

To be considered PR, patients must exhibit the following features for at least 2 months from end of treatment:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pre-treatment value

AND either a

[a] Bone marrow biopsies should be performed at least 2 months after the last treatment and if clinical and laboratory results demonstrate that a CR has been achieved.

- ≥ 50% reduction in lymphadenopathy (sum of longest diameter of the 6 largest lymph nodes by physical examination and 50% reduction in the sum of product of diameter of the 6 largest lymph nodes measured by CT scan). No increase in any node and no new enlarged lymph node. In small lymph nodes (< 2 cm in diameter), an increase of less than 25% is not considered to be significant.

OR

- ≥ 50% reduction of liver enlargement if enlarged at baseline as assessed by CT scan

OR

- ≥ 50% reduction of spleen enlargement if enlarged at baseline as assessed by CT scan

Plus at least 1 of the following:

- Neutrophils > 1.5×10^9/L [1500/μL] (without growth factors) or ≥ 50% increase of pretreatment value
- Platelets > 100×10^9/L (100000/μL) (without platelet transfusion growth factors) or ≥ 50% increase of pretreatment value
- Hemoglobin > 110 g/L (11 g/dL) (without blood transfusions or erythropoietin) or ≥ 50% increase of pre-treatment value

Partial Response with Lymphocytosis (PR-L)

Patients achieved PR with CLL-related signs or symptoms other than lymphocytosis will be considered PR-L and continue on therapy until the occurrence of definitive disease progression other than lymphocytosis alone.

Progressive Disease (PD)

PD during or after therapy will be characterized by at least 1 of the following:

- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5×10^9/L. During treatment, the increase should be assessed against baseline using a Day 1 (pre-cycle) nadir lymphocyte count and not interim cycle lymphocyte counts, which may not be stable. After treatment, increases should be assessed against the end of treatment response assessment.
- Appearance of new palpable lymph nodes (> 15 mm in longest diameter) or any new extra nodal lesion (regardless of size)
- ≥ 50% increase in the longest diameter of any previous site of clinically significant lymphadenopathy (ie, any lesion > 10 mm at baseline). During treatment, the increase should be assessed against baseline. After treatment, increases should be assessed against the end of treatment response assessment.
- ≥ 50% increase in the enlargement of the liver and/or spleen as determined by measurement below the relevant costal margin or appearance of palpable hepatomegaly or splenomegaly that was not previously present. During treatment, the increase should be assessed against baseline. After treatment, increases should be assessed against the end of treatment response assessment.
- Transformation to a more aggressive histology (eg, Richter's syndrome or plasmacytoid lymphocytic lymphoma with > 55% prolymphocytes). Whenever possible, this diagnosis should be supported by lymph node biopsy.

- After treatment, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by either:
  - A decrease of hemoglobin levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL)

  OR
  - a decrease of platelet counts by more than 50% or to less than 100 × 109/L (100000/μL), which occurs no earlier than 3 months after end of therapy defines progression if the marrow biopsy demonstrates an infiltration of clonal CLL cells.

Stable Disease (SD)

Patients who have not achieved a CR or a PR, or who have not exhibited PD, will be considered to have SD.

Objective response rates (ORRs) classified into classical ORR defined as the proportion of patients with CR, CRi, nPR, or PR, as determined by the investigator; and neo-ORR defined as the proportion of patients with CR, CRi, nPR, PR-L, or PR, as determined by the investigator.

Source: Adapted from Hallek et al 2008 and Cheson et al 2012.

APPENDIX 5 CONSENSUS-BASED UNIFORM RESPONSE CRITERIA FOR WALDENSTRÖM'S MACROGLOBULINEMIA

Developed by the IWWM, updated in the Sixth IWWM

Response Category	Description
Complete response	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response	• Monoclonal IgM protein is detectable • ≥ 90% reduction in serum IgM level from baseline[a] • Complete resolution of extramedullary disease, ie, lymphadenopathy/ splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial response	• Monoclonal IgM protein is detectable • ≥ 50% but< 90% reduction in serum IgM level from baseline[a] • Reduction in extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor response	• Monoclonal IgM protein is detectable • ≥ 25% but < 50% reduction in serum IgM level from baseline[a] • No new signs or symptoms of active disease
Stable disease	• Monoclonal IgM protein is detectable • < 25% reduction and < 25% increase in serum IgM level from baseline[a] • No progression in extramedullary disease, ie, lymphadenopathy/splenomegaly • No new signs or symptoms of active disease
Progressive disease	• ≥ 25% increase in serum IgM level[a,b] from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

IgM = immunoglobulin M.

[a] Sequential change in IgM levels may be determined either by M-protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

[b] An absolute increase of 0.5 g/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.

Source: Adapted from Dimopoulos 2014

APPENDIX 6 LUGANO RESPONSE CRITERIA FOR HODGKIN AND NON-HODGKIN'S LYMPHOMA

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

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

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

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

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

APPENDIX 7 LISTS OF PROHIBITED DRUGS AND THOSE THAT SHOULD BE USED WITH CAUTION

Drugs that are known to be strong inhibitors of CYP3A4 that may increase exposure to HMPL-523 are as follows:

- boceprevir
- clarithromycin
- conivaptan
- elvitegravir RIT
- fluconazole
- grapefruit juice (double strength)*
- indinavir
- itraconazole
- ketoconazole
- lopinavir/ritonavir
- mibefradil
- nefazodone
- nelfinavir
- posaconazole
- ritonavir
- saquinavir
- telaprevir
- telithromycin
- tipranavir/RIT
- troleandomycin
- voriconazole

*Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits, eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL], half a grapefruit, or 1-2 teaspoons (15 g) of Seville orange marmalade daily).

Drugs that are known to be strong inducers of CYP3A4 are as follows:

- avasimibe
- carbamazepine
- enzalutamide
- enzalutamide
- mitotane
- phenobarbital
- phenytoin
- rifabutin
- rifampin
- St John’s wort

Drugs that are known to be sensitive substrates of CYP1A2, CYP2B6, CYP3A4, P-gp, BCRP, or MATE1/2-K and the corresponding substrates with a narrow therapeutic range are listed in the table below. Co-administration with HMPL-523 may affect the levels (increase or decrease) of these drugs. Patients should be counseled and monitored for changes in efficacy or toxicity of these drugs if given concomitantly with HMPL-523.

CYP Enzymes/ Transporter	**Sensitive Substrates**	**Substrates with Narrow Therapeutic Range**
CYP1A2	• Alosetron • Duloxetine • Melatonin • Ramelteon • Tacrine • Tizanidine	• Theophylline • Tizanidine
CYP2B6	• Bupropion • Efavirenz	None
CYP3A4	• Levomethadyl (LAAM) • Lomitapide • Lopinavir • Lovastatin • Lumefantrine • Lurasidone • Maraviroc • Midazolam • Midostaurin • Neratinib • Nisoldipine • Perospirone • Quetiapine • Ridaforolimus • Saquinavir • Sildenafil • Simeprevir • Simvastatin • Sirolimus • Tacrolimus	• Alfentanil • Astemizole • Cisapride • Cyclosporine • Dihydroergotamine • Ergotamine • Fentanyl • Pimozide • Quinidine • Sirolimus • Tacrolimus • Terfenadine
P-gp	• Aliskiren • Ambrisentan • Dabigatran • Fexofenadine • Maraviroc • Talinolol • Tolvaptan	• Colchicine • Digoxin • Everolimus • Sirolimus

CYP Enzymes/ Transporter	Sensitive Substrates	Substrates with Narrow Therapeutic Range
BCRP	• Rosuvastatin • Sulfasalazine	None
MATE1/2-K	• Metformin	None

Abbreviations: BCRP = breast cancer resistance protein; CYP = cytochrome P450 enzyme; MATE = multidrug and toxin extrusion; P-gp = P-glycoprotein

APPENDIX 8 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

APPENDIX 9 RAI STAGING SYSTEM FOR CHRONIC LYMPHOID LEUKEMIA

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood > 15000/mm^3 and > 40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III	Stage 0-II with hemoglobin< 11 g/dL or hematocrit < 33%	High
IV	Stage 0-III with platelet < 100000/mm^3	High

Source: Adapted from Rai 1975

APPENDIX 10 BINET STAGING SYSTEM FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Binet classification:

- **Clinical stage A*** CLL is characterized by no anemia or thrombocytopenia and fewer than 3 areas of lymphoid involvement (Rai stages 0, I, and II).
- **Clinical stage B*** CLL is characterized by no anemia or thrombocytopenia with 3 or more areas of lymphoid involvement (Rai stages I and II).
- **Clinical stage C** CLL is characterized by anemia and/or thrombocytopenia regardless of the number of areas of lymphoid enlargement (Rai stages III and IV).

*Lymphoid areas include cervical, axillary, inguinal, liver, and spleen.

Adapted from Aronson et al 2022

APPENDIX 11 ANN ARBOR CLASSIFICATION

Revised staging system for primary nodal lymphomas

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

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

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

Source: Adapted from Cheson et al 2014

APPENDIX 12 INTERNATIONAL PROGNOSTIC INDEX

Follicular Lymphoma International Prognostic Index

Risk Factors	
Ann-Arbor Stage III or IV	
Age ≥ 60 years	
Serum LDH >1 × ULN	
Anemia (hemoglobin < 120 g/L)	
Involved nodal areas >4	
FLIPI Risk Group	**Number of FLIPI Risk Factors**
Low	0 or 1
Intermediate	2
High	3-5

Abbreviations: FDG = fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; PET = positron-emission tomography; ULN = upper limit of normal.
Note: The results of FDG-PET should not be taken into account for calculation of FLIPI, as this prognostic score was established without FDG-PET.
Source: Adapted from Solal-Celigny et al 2004.

Diffuse Lymphoma International Prognostic Index

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

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PET = positron-emission tomography; ULN = upper limit of normal.
Note: The results of FDG-PET should not be taken into account for calculation of IPI, as this prognostic score was established without FDG-PET.
Source: Adapted from Shipp et al 1993.

Simplified Mantel Cell Lymphoma International Prognostic Index Score

The simplified MIPI score will be derived based on baseline values of 4 prognostic factors: age, and Eastern Cooperative Oncology Group (ECOG), lactate dehydrogenase, and white blood cells. Points will be assigned to each of these factors as presented below, and the score will be derived by adding the points for all 4 factors. A score of 0-3 indicates low risk, 4-5 indicates intermediate risk, and 6-11 indicates high risk.

Prognostic Factors	**0 Points**	**1 Point**	**2 Points**	**3 Points**
Age (years)	<50	50-59	60-69	≥70
ECOG	0-1	Not applicable	2-4	Not applicable
LDH (relative to ULN, ie, LDH/ULN)	<0.67	0.67-0.99	1.0-1.49	≥1.5
WBC ($\times 10^9$/L)	<6.7	6.7-9.9	10.0-14.9	≥15.0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ULN = upper limit of normal; WBC = white blood cells.
Source: Adapted from Hoster et al 2008

International Prognostic Scoring System for Waldenström's Macroglobulinemia

Risk Factors	
Age >65 years	
Hemoglobin ≤11.5 g/dL,	
Platelet count ≤100×10^9/L	
Beta 2-microglobulin >3 mg/L	
Serum monoclonal protein concentration >7.0 g/dL	
IPI Risk Group	**Number of IPI Risk Factors**
Low	≤1 adverse characteristic and^#≤65 years old
Intermediate	2 adverse characteristics or only >65 years old
High	>2 adverse characteristics

Abbreviations: IPI = International Prognostic Index.

APPENDIX 13 CLINICAL EVALUATION OF POSSIBLE DRUG-INDUCED LIVER INJURY

If alanine aminotransferase (ALT) or aspartate aminotransferase (AST) is elevated to higher than 3 × upper limit of normal (ULN) **and** bilirubin is elevated to higher than 2 × ULN, HMPL-523 treatment should be discontinued immediately, and supportive treatment should be given. This combination of laboratory abnormalities meets the biochemical criteria for Hy's Law, which is associated with a markedly increased possibility of severe drug-induced liver injury (DILI) and may progress to liver transplantation or death (FDA 2009).

If the biochemical criteria for Hy's Law are met, HMPL-523 should be immediately discontinued, and patients need to be very closely monitored (bilirubin, alkaline phosphatase (ALP), AST, and ALT measured 2-3 times weekly until the results return to baseline or normal) and other causes of liver injury evaluated (eg, new or worsening hepatobiliary metastases; nonmalignant biliary obstruction; viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis; preexisting or acute liver disease; ischemic liver injury; right-sided congestive heart failure; new or worsening liver metastases; or concomitant medication that could cause the observed injury). Consultation with a gastroenterologist or hepatologist should be considered.

If the biochemical criteria for Hy's Law have been met, expedited reporting is required (see Section 6.5.2), before waiting for the evaluation of other causes to be completed.

Recommended Data Collection for Suspected DILI

The investigator is recommended to obtain the following information so as to further evaluate, follow up and complete the clinical data. Data should be recorded on case report forms (CRFs), where possible, and supplemented by investigator reporting as text in the clinical database:

- Medical history of the patient:
  - Detailed history of current symptoms, diagnosis of complications, and medical history
  - Previous medical history (viral hepatitis, alcoholic hepatitis, autoimmune disease, biliary tract disease, cardiovascular disease, etc)
  - History of concomitant medication (including over-the-counter and prescription drugs, herbal medicines, and dietary supplements), alcohol consumption, recreational drugs, and special diet
  - History of exposure to potentially hepatotoxic chemicals
- Complete the following laboratory tests:
  - Hematology
  - Clinical biochemistry: ALT, AST, bilirubin (including total bilirubin and direct bilirubin), ALP, albumin, prothrombin time or international normalized ratio, amylase, fasting blood glucose, cholesterol, and triglycerides
  - Other serum tests: Hepatitis A (anti-immunoglobulin M [IgM] and anti-IgG), hepatitis B (hepatitis B surface antigen, anti-HBs and hepatitis B virus deoxyribonucleic acid), hepatitis C (anti-hepatitis C virus [HCV]; HCV ribonucleic acid test is required for any patient with a positive test result), hepatitis D (anti-IgM and anti-IgG), hepatitis E (anti-HEV and anti-HEV IgM), and CMV (CMV DNA test is required for any patient with a positive test result).

- Complete appropriate auxiliary examination:
  - Patients with confirmed elevation of ALT/AST combined with total bilirubin are required to receive abdominal ultrasonography or other clinically applicable imaging examination within 48 hours (to exclude biliary tract, pancreatic, or intrahepatic causes, such as new or worsening hepatobiliary metastases or biliary calculi) and obtain the liver imaging result as soon as possible. If an alternative cause (such as biliary tract, pancreatic, or intrahepatic causes) of abnormal hepatic results cannot be confirmed by imaging, paracentesis is recommended for pathological examination after obtaining consent of the patient.
  - If suspected cardiovascular causes exist, cardiac ultrasonography is recommended to exclude cardiovascular dysfunction (ie, right heart failure).

Long-term follow-up: Perform close monitoring on the patient through repetitive tests of ALT, AST, ALP, and bilirubin (including total bilirubin and direct bilirubin) 2 to 3 times weekly until the laboratory ALT and/or AST abnormality becomes stable or recovers, and then proceed according to the protocol.

CCI

[redacted]

CCI [redacted]

APPENDIX 15 RECOMMENDATIONS FOR MANAGEMENT OF TOXICITY INCLUDING DOSE MODIFICATION

This document provides guidance to the investigators for the differential diagnosis and management of the important potential class toxicities noted on HMPL-523 trials and/or those associated with other SyK inhibitors. This constitutes general recommendations to investigators involved in HMPL-523 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 the following tables for the dose modification and toxicity management recommendations for pulmonary toxicities, gastrointestinal toxicities such as infectious diarrhea/colitis, nausea/vomiting, hepatic AEs, infection, neutropenia, thrombocytopenia, anemia, rash and cutaneous skin reactions.

As a general principle, the recommendations are as follows:

- Differential diagnosis for any adverse event should be diligently evaluated according to standard medical practice.
- Recommendations provided here should be evaluated in conjunction with the local clinical standard of care, and overall management plan should be clearly documented and 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.
- *For events that are clearly immune-mediated, prompt initiation of steroids and gradual tapering of steroids once event has resolved is recommended.*

Table 6 Dose Modification/Toxicity Management Recommendations for Pulmonary Toxicities (Including Pneumonia/Pneumonitis)

Adverse Reaction CTCAE v5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Followup
Grade 1 (Asymptomatic, clinical, or radiological observations only)	• Educate patient to report any new respiratory symptoms (dyspnea, cough) immediately • Monitor for symptoms including SpO2 measurement (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 noninfectious/immune-mediated pneumonitis • If persistent stable radiologic changes and asymptomatic on 1 to 2 scans, revert to normal restaging scans per protocol • If study drug withheld and 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 symptoms immediately • Monitor for worsening symptoms (eg, dyspnea/exertional dyspnea, cough) 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: ○ Infectious panel (consider cultures/PCR for bacterial, viral, and opportunistic infections, including PJP and CMV) ○ Chest X-ray, SpO2, and HRCT ○ PFT and BAL, as necessary ○ ILD markers (KL-6 and SP-D), if available	**Withhold study drug**	• Continue close follow-up and re-imaging, as needed • If considered infectious etiology or if the etiology is unclear: ○ If resolved in ≤7 days, resume study drug at same dose ○ If resolved in > 7 to 28 days, resume study drug at the same or a reduced dose at the discretion of the investigator – If symptoms recur at the original dose, then restart study drug at a reduced dose at resolution – If symptoms recur at the reduced dose, then permanently discontinue the study drug ○ If not resolved within 28 days or worsens, consider permanently discontinuing study drug • If considered immune-related and related to study treatment, promptly start systemic steroid

Adverse Reaction CTCAE v5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Followup
	○ COVID-19 testing (RT-PCR), if clinically indicated • If determined as infectious, prompt antibiotic, antifungal, or appropriate treatment as per standard guidelines • If determined as immune-related, promptly consider systemic steroid treatment ○ Administer methylprednisolone IV 1 to 2 mg/kg/day or equivalent oral corticosteroid dose		treatment, and permanently discontinue study drug ○ After sustained clinical improvement with steroid treatment is observed, gradually taper steroids (eg, 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 (eg, prednisone) during the steroid taper • Monitor closely on restarting treatment (regardless of whether pulmonary event is infectious or immune mediated); ○ If symptoms recur at the original dose, then restart study drug at a reduced dose at resolution ○ If symptoms recur at the reduced dose, then permanently discontinue the study drug

Adverse Reaction CTCAE v5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Followup

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 immunerelated 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
			• If considered infectious etiology or if the etiology is unclear:
			  ○ If resolved to baseline within 28 days, resume study drug at a reduced dose
			  ○ If not resolved to baseline within 28 days, permanently discontinue study drug
			  ○ If recurs on restarting treatment, permanently discontinue study drug
			• If considered immune-related:
			  ○ 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 (eg, 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 (eg, 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; PCR = polymerase chain reaction; 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 GI Toxicities

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:**
			  ○ **No change in study drug dose**
			  ○ Monitor as clinically indicated until complete resolution
			• **If not responsive to antidiarrheal treatment or worsening**
			  ○ **Withhold study drug**
			  ○ 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 noninfectious (ie, immune mediated), promptly start (including gradual tapering) enteric acting steroids (eg, 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
			  ○ **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):**
			  ○ **If event 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 immune mediated, promptly start steroid treatment with gradual tapering of steroids and resume study drug at a reduced dose if resolved to Grade 1 or baseline as described above**

Adverse Reaction CTCAE v5.0 Grade/Severity	**Recommended Management**	**Recommended Dosing Modification**	**Recommended Follow-up**
			• **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	**Withhold study drug**	• Continue close follow-up until resolution • Once resolved, start with reduced dose • If immune mediated, permanently discontinue study drug and promptly start steroid treatment with gradual steroid tapering • **Monitor closely on restarting treatment of the diarrhea/colitis regardless of whether infectious or immune mediated; if at the reduced dose, the symptoms recur at Grade 3 or higher, then permanently discontinue the study drug**

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-19 infection [use RT-PCR for diagnosis]) • Close monitoring for worsening of any clinical signs/symptoms (eg, 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**	• Monitor as clinically indicated and initiate treatment as per standard of care.

Grade 3 or 4 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 (ie, 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 recommend restarting at a reduced dose
			• **In case of Hy's Law or if suspicious of liver injury permanently discontinue study drug**

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 CMV 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 DNA > 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** • **In case of asymptomatic CMV viremia, may resume study drug at the same or a reduced dose at the discretion of the investigator if viral load is negative within 28 days**

Adverse Reaction CTCAE v5.0 Grade/Severity	**Recommended Management**	**Recommended Dosing Modification**	**Recommended Follow-up**
Shingles (Herpes zoster reactivation) Grade 1 or 2 infection	• Initiate antiviral therapy with acyclovir or valacyclovir	**Continue current dose**	• In case of persistent or worsening infection, manage as next higher grade
Shingles (Herpes zoster reactivation) Grade ≥ 3 infection	• Initiate antiviral therapy with acyclovir IV • Consider infectious disease consult to guide antiviral therapy	**Withhold study drug**	• Transition to oral antiviral therapy once stabilized • Consider **as clinically indicated** continuing antiviral prophylaxis with acyclovir or valacylovir, particularly during prolonged neutropenia • **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**
Pneumocytis jiroveci infection	• Consider pulmonary consult and bronchoscopy. Start empiric treatment (also refer to management of pulmonary toxicities)	**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 $\geq 1 \times 10^9$/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 $< 0.5 \times 10^9$/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 $\geq 1 \times 10^9$/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 Anemia

Adverse Reaction CTCAE v5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 3 Anemia (Hemoglobin < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L)	• Transfusion is indicated, especially if symptomatic	**Withhold study drug**	• **On resolution to ≤Grade 2 or baseline, resume at the same dose level or at the next lower dose level at the discretion of the investigator** • **In case of recurrence after restarting treatment, resume at the next lower dose level**
Grade 4 Anemia (Life-threatening consequences; urgent intervention indicated)	• Transfusion urgently indicated • Monitor with complete blood count at least every 2 weeks	**Withhold study drug**	• **On resolution to ≤Grade 2 or baseline, resume at the next lower dose level at the discretion of the investigator** • **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 13 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 • 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 does not 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 after dose reduction, 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.

Table 14 Dose Modification/Toxicity Management Recommendations for Nausea/Vomiting

Adverse Reaction CTCAE v5.0 Grade/Severity	Recommended Management	Recommended Dosing Modification	Recommended Follow-up
Grade 1 or 2 Nausea or vomiting	• Initiate dietary modification (small frequent meals, bland foods, sipping/eating slowly) • Initiate antiemetic therapy as needed	**Continue current dose**	• Reassess within 48 hours of starting supportive treatment • **If responsive to antiemetic treatment:** ○ **No change in study drug dose** ○ Monitor as clinically indicated until complete resolution • **If not responsive to antiemetic treatment or worsening** ○ **Withhold study drug** ○ In case of worsening, treat as Grade 3 or 4
Grade 3 Nausea or vomiting	• Initiate antiemetic therapy • IV hydration • Consider hospitalization • If persistent despite maximal supportive care and dose hold, investigate other causes (consider GI consult, imaging, CNS imaging)	**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, resume study drug at reduced dose** • **Consider using scheduled antiemetic prior to HMPL-523 administration for prophylaxis**
Grade ≥ 4 Vomiting	• Initiate antiemetic therapy IV • IV hydration • Hospitalization for stabilization/management • If persistent despite maximal supportive care and dose hold, investigate other causes (consider GI consult, imaging, CNS imaging)	**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, resume study drug at reduced dose** • **Consider using scheduled antiemetic prior to HMPL-523 administration for prophylaxis**

CTCAE = Common Terminology Criteria for Adverse Events; CNS = central nervous system; GI = gastroenterology; IV = intravenous.

APPENDIX 16 PROHIBITED CONCOMITANT MEDICATIONS THAT HAVE A KNOWN RISK OF QT PROLONGATION AND/OR TORSADES DE POINTES (TDP)

Generic Name	Brand Names (Partial List)	Drug Class
Aclarubicin	Aclacin and others	Anticancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Trisenox	Anticancer
Astemizole	Hismanal	Antihistamine
Azithromycin	Zithromax, Zmax	Antibiotic
Bepridil	Vascor	Antihypertensive
Cesium Chloride	Energy Catalyst	Unclassified
Chloroquine	Aralen	Antimalarial
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Chlorprothixene	Truxal	Antipsychotic
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic
Cisapride	Propulsid	Gastroprokinetic agent
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Clarithromycin	Biaxin, Prevpac	Antibiotic
Cocaine	None	Local anesthetic
Disopyramide	Norpace	Antiarrhythmic
Dofetilide	Tikosyn	Antiarrhythmic
Domperidone	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea
Donepezil	Aricept	Cholinesterase inhibitor
Dronedarone	Multaq	Antiarrhythmic

Generic Name	Brand Names (Partial List)	Drug Class
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic/Antiemetic
Erythromycin	E.E.S and others	Antibiotic
Escitalopram	Cipralex, Lexapro, Nexito,	Antidepressant, SSRI
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic
Fluconazole	Diflucan, Trican	Antifungal
Gatifloxacin	Tequin	Antibiotic
Grepafloxacin	Raxar	Antibiotic
Halofantrine	Halfan	Antimalarial
Haloperidol	Haldol	Antipsychotic
Hydroquinidine	Serecor	Antiarrhythmic
Hydroxychloroquine	Plaquenil and others	Antimalarial
Ibogaine	None	Psychedelic
Ibutilide	Corvert	Antiarrhythmic
Levofloxacin	Levaquin, Tavanic	Antibiotic
Levomepromazine (Methotrimeprazine)	Nosinan and others	Antipsychotic
Levomethadyl acetate	Orlaam	Opioid agonist
Levosulpiride	Neoprad, Lesuride and others	Antipsychotic, prokinetic agent
Meglumine antimoniate	Glucantime	Antileishmanial
Mesoridazine	Serentil	Antipsychotic
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist
Mobocertinib	Exkivity	Anticancer
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic

Generic Name	**Brand Names (Partial List)**	**Drug Class**
Nifekalant	Shinbit	Antiarrhythmic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic
Oxaliplatin	Eloxatin	Antineoplastic agent
Papaverine	Multiple	Antispasmodic
Pentamidine	Pentam	Antifungal
Pimozide	Orap	Antipsychotic
Probucol	Lorelco	Antihyperlipidemic
Procainamide	Pronestyl, Procan	Antiarrhythmic
Propofol	Diprivan, Propoven	Anesthetic, general
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic
Roxithromycin	Rulide and others	Antibiotic
Sertindole	Serdolect and others	Antipsychotic
Sevoflurane	Ultane, Sojourn	Anesthetic, general
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic
Sparfloxacin	Zagam	Antibiotic
Sulpiride	Dogmatil and others	Antipsychotic
Sultopride	Barnetil, Topral and others	Antipsychotic
Terfenadine	Seldane	Antihistamine
Terlipressin	Teripress and others	Vasoactive agent
Terodiline	Micturin and others	Antispasmodic
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic
Vandetanib	Caprelsa	Anticancer

APPENDIX 17 EUROPEAN UNION GENERAL DATA PROTECTION REGULATION- AND CLINICAL TRIAL REGULATION-COMPLIANT DATA PROTECTION

HUTCHMED Limited, as Data Controller of this study, ensures that all processing activities involving personal data performed in the scope of the study comply with applicable privacy and data protection laws, including, but not limited to, Regulation (EU) 2016/679 (General Data Protection Regulation), together "Data Protection Laws."

HUTCHMED Limited will ensure that the technical, organizational, and contractual security measures described below are periodically reviewed and updated to take into account relevant technological developments and/or changes to the processing of personal data in conjunction with the study. All locations, personnel, and information systems that are used to perform services for the study will be covered by the measures described in this appendix.

HUTCHMED Limited may apply additional statutory measures where required by the national laws that apply to the study or that HUTCHMED Limited otherwise deems appropriate, and in such cases, it will implement these measures even if they are not expressly listed below.

Technical Measures

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors
- Ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the study ("role-based access")
- The pseudonymization and encryption of personal data, as appropriate
- Processing personal information in accordance with the data minimization principle, meaning that personal data is never collected "just in case" and each data element collected is necessary for the purpose of conducting the study
- The ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services
- Network, application, and database security by means of firewalls and antivirus/antimalware
- Ensuring the detection of malware purposed for unauthorized deletion, blocking, copying of information, or disabling security measures
- The means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident
- Logging of security events/incidents in information systems and implementation of system audit trails, where applicable
- Ensuring that information systems, computers, and software involved in the performance of the services provided in the study are backed up
- A process for regularly testing, assessing, and evaluating the effectiveness of technical measures

- Procedures to detect any personal data breach that may occur

Study subjects will be assigned a subject identification number for the purposes of transferring their personal data, and names or other information that would make study subjects directly identifiable will not be transferred. The information technology systems used to collect, process, and store study-related data are secured by the technical, organizational, and contractual security measures described in this appendix, in particular so that identifiable personal data of study subjects are not processed other than as contemplated by the protocol.

Sponsor representatives acting on behalf of HUTCHMED Limited will have read-only access to fully identifiable personal data only when strictly necessary, eg, in the scope of the on-site monitoring visits and audits, only for the source data verification mandatory under the clinical study framework, including the ICH-GCP obligations applicable to the conduct of the study.

In addition, records containing fully identifiable personal data may be reviewed by national and international regulatory authorities.

Organizational Measures

HUTCHMED Limited has implemented and maintains the following organizational measures:

- The provision of information notices to, and where required, obtaining consent from, data subjects (including the participants in the study)
- Procedures and practices for data protection compliance, including policies and standard operating procedures relating to personal data security, data subject rights requests, data retention, personal data breaches, vendor contracting, and transfer impact assessments
- Procedures and practices for securing the destruction of paper documents containing personal data after the applicable retention period, if any
- Procedures and practices that cover reporting, analysis, monitoring, and resolution of security incidents
- Business continuity procedures and practices to help ensure that HUTCHMED Limited can continue to provide services through operational interruption
- Processes to ensure that cross-border transfers of personal data comply with the Data Protection Laws
- Procedures and practices for employee and staff awareness and training
- Procedures and practices for auditing compliance with the Data Protection Laws

Contractual Measures

When selecting vendors, HUTCHMED Limited has due diligence processes in place. In addition to the above-mentioned technical and organizational measures, HUTCHMED Limited, by means of internal measures and imposing contractual data processing clauses on relevant subcontractors and third parties, ensures the confidentiality of records and personal data of study subjects. In addition, the contracts between the Sponsor and study sites specify the responsibilities of the parties relating to data protection, including the handling of personal data breaches, respective communication, and cooperation of the parties.

Personal Data Breaches

HUTCHMED Limited has put in place a process to assess and, if required, report personal data breaches occurring at its or its subcontractors' facilities and premises. In the event of a data breach, HUTCHMED Limited will apply appropriate measures to mitigate the risks to data subjects based on the specific context of the data breach and taking into account the rights and freedoms of the individuals. If a breach is likely to result in a risk to data subjects, HUTCHMED Limited will determine whether it is required to notify the applicable supervisory authorities within 72 hours after becoming aware of the breach, and if the breach is likely to result in a high risk to data subjects, the relevant individuals will also be informed without undue delay. In addition, HUTCHMED Limited will take appropriate steps to mitigate the possible adverse effects of the data breach in coordination with the relevant parties involved in the study (whether controllers and/or processors) and those parties' data protection officers.

Data Transfer

Where applicable, personal data may be transferred to third countries outside of the European Economic Area. HUTCHMED Limited ensures the security of the data transfer by means of an Adequacy Decision, where applicable, or by concluding Standard Contractual Clauses as provided by the European Commission in adjunction with appropriate supplementary measures. A Transfer Impact Assessment will be in place before the first subject data is processed.

APPENDIX 18 AMENDMENT HISTORY

Amendment 4 (12 December 2022)

Section Number	Summary of Change	Rationale for Change
Cover Page, Sponsor's Approval, Document History, Header, and Footer	Administrative updates made to reflect Amendment 4	The administrative updates were made to reflect Amendment 4.
Section 2.1 – Current Therapies and Unmet Medical Need	Additional text added to review the use of BCL-2 inhibitor therapy in CLL and definition of double refractory CLL	This information clarifies the current treatment landscape in CLL and provides background for requirement for prior BCL-2 inhibitor therapy in selected patients in the post-BTK CLL cohort.
Section 2.2.3 – Nonclinical Toxicology	Additional text added to update results of in vitro phototoxicity studies	Based on updated data
Synopsis, Section 4.5 – Dose Expansion Stage (Stage 2)	Language was added to indicate that as of 30 November 2022, patients will no longer be permitted to consent to enroll in selected lymphoma dose expansion cohorts (mantle cell lymphoma [MCL], follicular lymphoma [FL], marginal zone lymphoma [MZL], Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma [WM/LPL], peripheral T-cell lymphoma [PTCL], and cutaneous B-cell lymphoma [CBCL]. Currently enrolled patients deriving clinical benefit from treatment may continue to participate in the study. The dose expansion cohort for chronic lymphocytic leukemia (CLL) post-Bruton tyrosine kinase (BTK) exposure is also modified to require approximately 10 out of 20 patients to have received prior Bcell lymphoma-2 (BCL-2) inhibitor therapy in addition to the BTK therapy.	This new language confirms that consenting to the study, for selected cohorts was halted on 30 November 2022. 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. Based on emerging unmet need in the clinic for the management of patients who have failed both BTK and BCL-2 targeted therapies, so called "double refractory" patients
Synopsis, Section 4.7.2 – Rationale for Selection of Patient Population, Section 5.1.1 – Inclusion Criteria	Language regarding closing enrollment to all non-Hodgkin's lymphoma (NHL) expansion cohorts added.	This language was added to reflect changes in patient enrollment upon implementation of this protocol amendment.
Synopsis, Section 4.8.3 – Pharmacokinetic Outcome Measures	Removed bullet "The Accumulation Index based on area under the concentration time curve (AUC)"	Clarification
Section 5.4.3 – Recommendations for Management of Toxicity Including Dose Modification	Removed phototoxicity management/sunlight precautions	Results of the in vitro phototoxicity studies with HMPL-523 CCI CCI showed no phototoxic potential, indicating

Section Number	Summary of Change	Rationale for Change
		that the previously necessary precautions in this clinical study can be lifted.
Synopsis, Section 7.1 – Determination of Sample Size, Section 7.1.2 – Stage 2: Dose Expansion	Language was added to confirm the total expected enrollment is approximately 90 patients and approximately 70 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.
Section 7.2 – Analysis Population	Text added defining DLT evaluation	Based on updated data
Synopsis, Section 7.3 – Analysis Planned, Section 7.3.1 – Demographic and Baseline Characteristics, Section 7.3.2 – Disposition of Patients Enrolled in the Study, Section 7.3.3 – Safety Analysis, Section 7.3.3.2 – Adverse Events, Section 7.3.3.3 – Clinical Laboratory Test Values, Section 7.3.3.4 – Vital Signs, Section 7.3.3.5 – 12-Lead ECGs, Section 7.3.5 – Efficacy Analysis	Any language, headings, tables, and analyses related to assessments, objectives, and endpoints that fall outside of the scope of the necessary assessments for the Safety Review Committee to monitor the benefit/risk profile of patients remaining on trial were updated or removed.	This language was updated or removed to clarify what assessments, objectives, and endpoints are still relevant upon implementation of this protocol amendment.

Amendment 3 (23 July 2022)

Section Number	Summary of Change	Rationale for Change
Section 2.1 – Current Therapies and Unmet Medical Need Section 2.2.2 - Nonclinical Pharmacokinetics Section 2.2.3 - Nonclinical Toxicology Section 2.2.4 – Clinical Experience Section 2.3.2.1 – Risk Assessment	Updated based on Investigator's Brochure (IB) v9.	To provide updated information.
Section 4.5 Dose Expansion Stage (Stage 2)	Overall expansion stage enrollment increased from 110 to 125. Increased number of patients in Hodgkin's lymphoma (HL) cohort of expansion stage from 10 to 25.	To increase the sample size of the HL dose expansion cohort to further evaluate the efficacy and safety of HMPL-523 in these patients.
Section 4.7.1 - Rationale for the Starting Dose and the Dose Schedule	Updated status of studies as of 10 May 2022.	To provide updated information.
Section 5.1.1 – Inclusion Criteria #4	Added number of subjects for HL cohort.	To increase the sample size of the HL dose expansion cohort to further

Section Number	Summary of Change	Rationale for Change
		evaluate the efficacy and safety of HMPL-523 in these patients.
Section 5.1.2 – Exclusion Criteria #2	Note has been updated to clarify patients with low complete blood cell count can be enrolled if they have splenic involvement or bone marrow infiltration.	To allow splenic involvement or bone marrow infiltration as condition with sponsor approval to make exception for lower blood counts.
Section 5.1.2 – Exclusion Criteria #14 Appendix 1 – Schedule of Activities Appendix 13 Clinical Evaluation of Possible Drug-Induced Liver Injury	Added cytomegalovirus (CMV) test at screening.	To provide clarification that CMV viral antibody test should be performed at screening to ensure CMV DNA testing is negative to enroll patients.
Section 5.1.2 – Exclusion Criteria #18 Section 5.5.2 – Prohibited Therapy and Food Appendix 16 - Prohibited Concomitant Medications that Have a Known Risk of QT prolongation and/or Torsades de Pointes (TdP)	Reference to http://www.crediblemeds.org removed and appendix has been added.	For clarification on prohibited concomitant medications that have a known risk of QT prolongation and/or TdP.
Section 5.4.3 and Appendix 15 Recommendations for Management of Toxicity Including Dose Modification	Added new section and appendix on recommendations for management of toxicity including dose modification.	To provide guidelines for management of toxicities including dose modifications.
Section 5.5.2 – Prohibited Therapy and Food	Updated the section.	To provide updated information based on findings and interpretation of in vitro drug-drug interaction studies.
Section 5.6.9 – Laboratory Assessments	Added CMV testing at screening. Removed reticulocyte count and bands as part of differential white blood cells count.	For clarification. Reticulocyte count and bands are not part of routine complete blood count at many sites.
Section 5.6.10 – Electrocardiogram Appendix 1 – Schedule of Activities	Electrocardiogram to be performed at screening and at Cycle 1, Day 1.	For clarification.
Section 5.7.3 – Study Treatment Discontinuation	Added cross reference to Section 5.5.2	For clarification.
Section 5.9.3 – Analytical Procedures	Updated the method for determination of chemokines.	For clarification.
Section 6.2.3 – Protocol-Defined Events of Special Interest Expedited Adverse Events	Added adverse events of special interest.	For clarification.
Section 7.1 – Determination of Sample Size Section 7.1.2 Stage 2: Dose Expansion	Planned enrollment for this study was updated from approximately 116 to 140 patients to approximately 131 to 155 patients.	To increase the sample size of the HL dose expansion cohort to further evaluate the efficacy and safety of HMPL-523 in these patients.

Section Number	Summary of Change	Rationale for Change
	Increased number of patients in HL cohort as noted above for Section 4.5. Sample size increased from 110 to 125 patients. Probability of observing at least 1 adverse event in expansion stage patients was updated.	
Section 7.2 – Analysis Population	Definition of response evaluable set (RES) updated.	For clarification.
Appendix 7 – Lists of Prohibited Drugs and Those That Should Be Used with Caution	Renamed/revised appendix and added P-gp, BCRP, and MATE1/2-K sensitive substrates and substrates with narrow therapeutic range.	To avoid confusion and protocol deviations for prohibited concomitant medications and to specify that the substrates with narrow therapeutic range are prohibited.
Throughout the protocol	Administrative changes made throughout the protocol.	To update company name, address, company logo, and amendment version.
Throughout the protocol	Minor grammatical, formatting, and revisions were made throughout the protocol.	For better presentation.

Amendment 2 (07 August 2021)

Section Number	Summary of Change	Rationale for Change
Section 4.5 - Dose Expansion Stage (Stage 2)	Overall expansion stage enrollment increased from 70 to 110. Addition of new cohorts: CLL/SLL post-BTK exposure (n = 20) and HL (n = 10). Increased number of patients in FL cohort of expansion stage from 10 to 20. Add identified RP2D (700 mg once daily).	To add a dose expansion cohort and increase the sample size of an existing dose expansion cohort to further evaluate the efficacy and safety of HMPL-523 based on proof of activity from a Phase I study in China evaluating HMPL-523 in lymphoma patients. For information.
Section 4.4.5 - Definition of Recommended Phase II Dose	Added identified RP2D (700 mg once daily).	For information.

Section Number	Summary of Change	Rationale for Change
Section 7.1 - Determination of Sample Size Section 7.1.2 - Stage 2: Dose Expansion	Addition of new CLL/SLL post-BTK exposure and HL cohorts and increased number of patients in FL cohort as noted above for Section 4.5. Provided updated probability of observing a given adverse event based on increase in number of patients in expansion phase. Sample size (planned enrollment) corrected to 116-140 patients.	To add a dose expansion cohort and increase the sample size of an existing dose expansion cohort to further evaluate the efficacy and safety of HMPL-523 based on proof of activity from a Phase I study in China evaluating HMPL-523 in lymphoma patients. To be consistent with 6-30 patients from dose escalation stage + 110 patients from dose expansion.
Section 2.2.4 - Clinical Experience Section 4.7.1 - Rationale for the Starting Dose and the Dose Schedule	Removed location "Australia" for 2015-523-00CH1, which was conducted in China.	For correction.
Section 2.2.4.5 - Study 2018-523-00US1 Phase I Study in Patients with Relapsed/Refractory Lymphoma	Subsection added to describe the rationale for adding the chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) post-Bruton's tyrosine kinase (BTK) exposure and Hodgkin lymphoma (HL) cohorts and increasing number of patients in follicular lymphoma (FL) cohort.	To provide rationale for additional expansion phase cohorts and to have a larger cohort to further evaluate the efficacy of HMPL-523 in FL.
Section 2.1 - Current Therapies and Unmet Medical Need	Added background regarding spleen tyrosine kinase expression in HL patients.	To provide rationale for addition of HL cohort.
Section 4.5.1 - Exploratory Analysis	Section deleted and content moved to Section 5.9.	To present sub-section in Section 5.9 for a better flow as the exploratory biomarker analysis applies to the entire study and not just the dose expansion stage.
Section 5.4.2 - After Dose-Limiting Toxicity Assessment Window in Stage 1 or in Stage 2	Specified 600 mg and 400 mg dose as the first and second lower dose in case of toxicity. Added statement to consult with Sponsor if treatment hold longer than 2 weeks is required for resolution of toxicity. Add requirement for additional PK sampling if dose is reduced for toxicity in Stage 2.	For clarification. To allow longer window for toxicity resolution. To evaluate relationship of PK data to observed toxicity.
Section 5.6.9 - Laboratory Assessments	Removed description of pharmacokinetic (PK) and pharmacodynamic assessments.	To minimize redundancy as these assessments are addressed separately under Section 5.9.

Section Number	Summary of Change	Rationale for Change
Section 5.9 - Pharmacokinetic and Pharmacodynamic Assessments	Revised/reorganized section. Previously Section 5.9 title was "Assay Methods." Included and updated text regarding exploratory analyses that was previously in Section 4.5.1. Reference to central laboratory removed. Method for analysis of plasma samples (Liquid Chromatography-Tandem Mass Spectrometry) identified.	To streamline and update the content.
Section 5.9.1 - Collection Schedule	Included collection of additional PK and pharmacodynamic samples for steady state reached with new dose after treatment hold for toxicity. Specified purpose for blood samples that remain after PK analysis. Include statement that tumor biopsy (archival or fresh biopsy) will be collected at screening for patients in dose expansion cohorts. Specified purpose for tumor samples that remain after predefined analysis.	To evaluate relationship of PK data to observed toxicity. For clarification. To allow evaluation of candidate biomarkers. For clarification.
Section 5.1.1 - Inclusion Criteria # 7	Added requirement for availability of tumor sample (archival or fresh biopsy) for patients in dose expansion cohorts.	To allow evaluation of candidate biomarkers.
Section 4.7.1 - Rationale for the Starting Dose and the Dose Schedule	Updated study status of clinical trials discussed. Updated Table 2 data.	To provide updated study status. To provide corrected data.
Section 4.7.2 - Rationale for Selection of Patient Population	Listed patients with CLL post-BTK exposure and HL with the rest of the cohorts. Replaced term "NHL" with "lymphoma."	To include new cohorts. To use more general term, since HL cohort has been added.
Section 5.3.5 - Post-Trial Access to HMPL-523	Replaced term "NHL" with "lymphoma."	To use more general term, since HL cohort has been added.

Section Number	Summary of Change	Rationale for Change
Section 4.8.3 - Pharmacokinetic Outcome Measures	Removed following PK parameters: • Terminal half-life • Apparent volume of distribution based on the terminal phase • Mean residence time • Mean plasma concentration	To update list of PK parameters.
Section 7.3.4 - Pharmacokinetic Analysis	Listed PK parameters updated as for Section 4.8.3. Added statement that statistical or PK analysis plan will source for details of PK analysis. Specified that HMPL-523 CCI concentrations will be plotted by dose level.	To update list of PK parameters and related endpoints. For clarification. For clarification.
Section 5.1.1 - Inclusion Criteria #4	Addition of CLL/SLL post-BTK exposure and HL cohorts.	To further evaluate the efficacy and safety of HMPL-523.
Section 5.1.1 - Inclusion Criteria #6	Clarified the definition of measurable disease to align with Lugano criteria: nodal disease > 1.5 cm, non-nodal disease > 1 cm. Added HL to disease subtypes listed in text describing measurable disease definition.	For consistency with Lugano criteria as the measurable disease was defined as > 1.5 cm. To include HL, as an HL cohort has been added to study.
Section 5.1.1 - Inclusion Criteria #10 Section 5.6.9 - Laboratory Assessments Appendix 1 - Schedule of Activities, footnote 16	For contraception, specified that male patients must use condom. Clarified measures to be used are highly effective measures as defined by Clinical Trials Facilitation Group, provided additional information regarding route of administration and types of contraceptive methods. Updated duration of contraceptive use from 100 days to 30 days (based on updated investigator's brochure [IB]). Clarified definition of postmenopausal female.	To align with updated recommendation in IB and to match other protocols.
Section 5.1.2 - Exclusion Criteria #15	Listed urine test under pregnancy test.	For clarification.

Section Number	Summary of Change	Rationale for Change
Section 2.2.1 - Nonclinical Pharmacology Section 2.2.2 - Nonclinical Pharmacokinetics Section 2.2.3 - Nonclinical Toxicology	Updated based on IB v8.	To provide updated information.
Section 2.2.4 - Clinical Experience	Updated based on IB v8.	To provide updated information.
Section 2.3 - Study Rationale and Benefit-Risk Assessment	Added subheadings within section. Added important identified risks provided in IB v8. Added reference to Section 2.2.4.	To provide updated information.
Section 5.7.1 - Study Completion/Early Termination Visit	Replaced “TEAE” with “AE”. Added “Extended Monitoring” to “Follow-up” subheading.	For correction. For clarification.
Appendix 14 Coronavirus Disease 2019 (COVID-19) Risk Assessment and Vaccine Guidance (New Appendix) Section 5.1.2 - Exclusion Criteria #12	Added appendix providing COVID-19 risk assessment and vaccine guidance. Added reference to COVID appendix.	For guidance on COVID-19 risk assessment and vaccination.
Section 5.5.2 - Prohibited Therapy and Food	Added restrictions and instructions on the use of acid-reducing agents. Added exception to grapefruit restriction based on Appendix 7.	To avoid co-administration of acid-reducing agents that may have a negative impact on the absorption of and decrease the bioavailability of HMPL-523 as the solubility of HMPL-523 is pH dependent. For clarification.
Section 5.6.2 - Informed Consent Forms and Screening Log Section 8.3 - Patient Information and Consent Section 8.4 - Data Privacy and Confidentiality	Included detailed information regarding data protection.	To comply with data privacy regulations/guidance.

Section Number	Summary of Change	Rationale for Change
Appendix 1 Schedule of Activities	Added row for screening tumor biopsy for patients in dose expansion cohorts. Added "pharmacodynamics" plasma sampling with PK plasma sampling under procedures. Footnote 22 revised: "All" rather than "some" expansion patients will provide samples for PD analysis; text regarding basis for defining scope of PD assessment and determination of PD sampling time points is deleted. Replaced "Cycle 1 Day 1" with "screening" for Footnote 6.	For analysis of candidate biomarkers. For clarification.
Appendix 2 PK Sampling Time Points (Once Daily) (Dose Escalation Stage)[d]	Removed column for "Sample Volume." Added footnote "d" specifying that the remaining blood samples may be used exclusively for exploratory biomarker purposes.	To avoid duplication and discrepancy as the sample volume can be found in the PK laboratory manual. For clarification.

Section Number	Summary of Change	Rationale for Change
Appendix 3 PK and Pharmacodynamics Sampling Time Points (Dose Expansion Stage)[e]	Removed column for "Sample Volume."	To avoid duplication and discrepancy as the sample volume can be found in the PK laboratory manual.
	Added 2 new columns for additional trough PK and pharmacodynamics samples to be collected in the dose expansion phase.	For analysis of long-term PK and pharmacodynamics results in patients receiving HMPL-523.
	Added additional PK and pharmacodynamic sampling visit day and timepoints after dose reduction due to toxicity.	To evaluate relationship of PK data to observed toxicity.
	Added footnotes "d" and "f" specifying recording of actual date and time of the PK samples in the electronic case report form, study drug intake at the investigative site under the supervision of the investigator or designee on PK sampling day. Added footnote "e" to specify use of blood samples remaining after PK analysis for exploratory biomarker purposes. Added footnote "g" for Cycle 1 Day 28 for PK sample rescheduling in case they are not collected as scheduled.	For clarification.
Section 6.7 - Post-Study Adverse Events	Revised term "congenital anomaly" to "congenital anomaly/birth defect."	For consistency with usage in other parts of protocol.
Section 6.4.10 - Pregnancy	Specified the last dose of the study drug as male patient's last dose of the study drug.	For clarification.
Section 7.3.6 - Biomarker Analysis	Replaced the information for biomarker analysis plan document with a high-level summary of the analysis to be performed.	For correction as the biomarker analysis plan document is not available.
Appendix 15 - Amendment History (New Appendix)	Added summary of Amendment 1 changes to Amendment History.	For consistency with sponsor's process and template.

Amendment 1 (09 April 2020)

Description and Rationale for Change	Sections
Updated the clinical cutoff date and inclusion of completed studies.	Section 2.2.4 Clinical Experience

Description and Rationale for Change	**Sections**
Ongoing studies have been updated to represent the appropriate countries.	
New section has been added for a Phase I open-label study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma.	Section 2.2.4.5 Study 2018-523-00US1 Phase I Study in Patients with Relapsed/Refractory Lymphoma
Updated to reflect the deletion of the 1000 mg dose and keeping the 600 mg dose.	Section 2.3 Study Rationale
Added an exploratory objective to explore biomarkers	Section 3.3 Exploratory Objectives
Added ongoing study information and updated safety data from completed dose escalation studies.	Section 4.7.1 Rationale for the Starting Dose and the Dose Schedule
Added peripheral T-cell lymphoma (PTCL) and cutaneous B-cell lymphoma (CBCL) to types of lymphoma patients that will be enrolled	Section 4.7.2 Rationale for Selection of Patient Population Section 5.1.1 Inclusion Criteria
Route of administration has been added to specify: Orally, with water, after meal Removed pharmacokinetic data from dose escalation decision Removed potential for BID dosing	Section 4.2 Dose Escalation Stage (Stage 1) Table 1 Proposed Dose Escalation Scheme
New section has been added to specify eligibility criteria for patient intradose-escalation	Section 4.3 Intrapatient Dose Escalation (new section)
Clarified definition of febrile neutropenia per CTCAE v5.0 and added criteria for Hy's Law	Section 4.4 Definition of a Dose Limiting Toxicity
Further clarified definition of DLT evaluable patients	Section 4.4.1 Dose Limiting Toxicity Assessment Window
Two additional cohorts have been added (PTCL and CBCL) with 10 patients planned for each of these cohorts. Revised the total number of patients from approximately 50 to approximately 70 patients with relapsed or refractory lymphomas	Section 4.5 Dose Expansion Stage (Stage 2) Section 5.1.1 Inclusion Criteria
Updated clinical trial information	Section 4.7.1 Rationale for the Starting Dose and the Dose Schedule
Added and clarified definitions of best overall response (BOR), time to response (TTR), and progression free survival (PFS).	Section 4.8.4 Efficacy Outcome Measures Section 7.3.5 Efficacy Analysis

Description and Rationale for Change	Sections
The inclusion criteria have been expanded to include the 2 additional cohorts: PTCL and CBCL. Clarified the definition of relapsed and refractory lymphoma patients as: e. 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. f. Those who can no longer tolerate/withstand cytotoxic chemotherapy and or available standard of treatment/care. Where safety profile and risks of toxicity of other treatment options far outweigh any possible clinical benefit g. Those with no curative standard of treatment or where available treatments are not reasonable or do not make sense. In particular, and in the opinion of the attending principal investigator, those who will benefit from this class of compound Contraceptive methods were clearly defined, and language has been added to describe highly effective measures. Moved exclusion regarding prior SYK inhibitors to the inclusion criteria section for clarification of language	Section 5.1.1 Inclusion Criteria
Revised the following exclusion criteria: • Amended laboratory abnormality parameters in exclusion criteria #2 • Changed estimated creatinine clearance (CrCl) per Cockcroft-Gault parameters for escalation stage • Added exclusion of patients that have used St. John's wort within 3 weeks of study initiation • Consolidated exclusion criterion #7 into #5 • Changed exclusion criterion #9 to clarify prohibited drugs and clarify exclusionary window for patients that have used these drugs prior to study initiation • Added patients with interstitial lung disease to exclusion criterion #13 • Removed exclusion criterion #24 from the protocol body to align with the synopsis Added the following exclusion criteria: • #24 Ongoing psychiatric disorder, specifically patient with depression and/or suicidal tendencies • #25 Patients with pathological fractures, especially with unknown etiology	Section 5.1.2 Exclusion Criteria
Simplified drug labeling procedure to avoid conflicting information	Section 5.3.2 Drug Labeling
Clarified the HMPL-523 dosing window and administration with food	Section 5.3.4 Dosage, Administration, and Compliance

Description and Rationale for Change	**Sections**
Clarified eligibility criteria for post-trial access to HMPL-523	Section 5.3.5 Post-Trial Access to HMPL-523
Added reference http://medicine.iupui.edu/clinpharm/ddis/main-table	Section 5.5 Concomitant Therapy and Food
Changed ECG requirement from screening and pre-dose to one or the other	Section 5.6.10 Electrocardiogram
Added +/-7 day window to tumor assessments to align with NTF issued to sites previously	Section 5.6.12 Tumor and Response Evaluation
Clarified intent of laboratory assessments window prior to initiating HMPL-523 dosing	Section 5.6.9 Laboratory Assessments
Added parameters to align with EMA guidance	Section 5.8 Study/Site Discontinuation and Closure
Removed DLT notification “form” to align with NTF issued to sites previously	Section 6.2.4 Reporting of Dose-Limiting Toxicity
Added a new analysis population, the response evaluable set	Section 7.2 Analysis Population
Added text to the planned analysis for clarity	Section 7.3 Analysis Planned
Added description of pharmacodynamics assessments for certain patients at the sponsor’s discretion	Section 5.9 Assay Methods
Added section describing the biomarker analysis	Section 7.3.6 Biomarker Analysis (new section)
Updated the Schedule of Activities to align with changes in this amendment	Appendix 1 Schedule of Activities
Added an Amendments column in the Version/Amendment History table for clarification	Version/Amendment History
Added a statement a statement of compliance according to ICH E6(R2) guidelines	Statement of Compliance (new section)
Revised the Investigator’s Agreement page for compliance with health authority requirements and consistency with the sponsor’s global study protocols	Investigator’s Agreement
Nonsubstantive editorial and formatting changes were made for administrative purposes or improvements in clarity.	Throughout entire document

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Approval Task	PPD

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