STATISTICAL ANALYSIS PLAN

2018-523-00US1

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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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 12Mar2025) for Protocol 2018-523-00US1.

	Name	Signature	Date (DDMMYYYY)
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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OUTPUT TEMPLATES SIGNATURE PAGE

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MODIFICATION HISTORY

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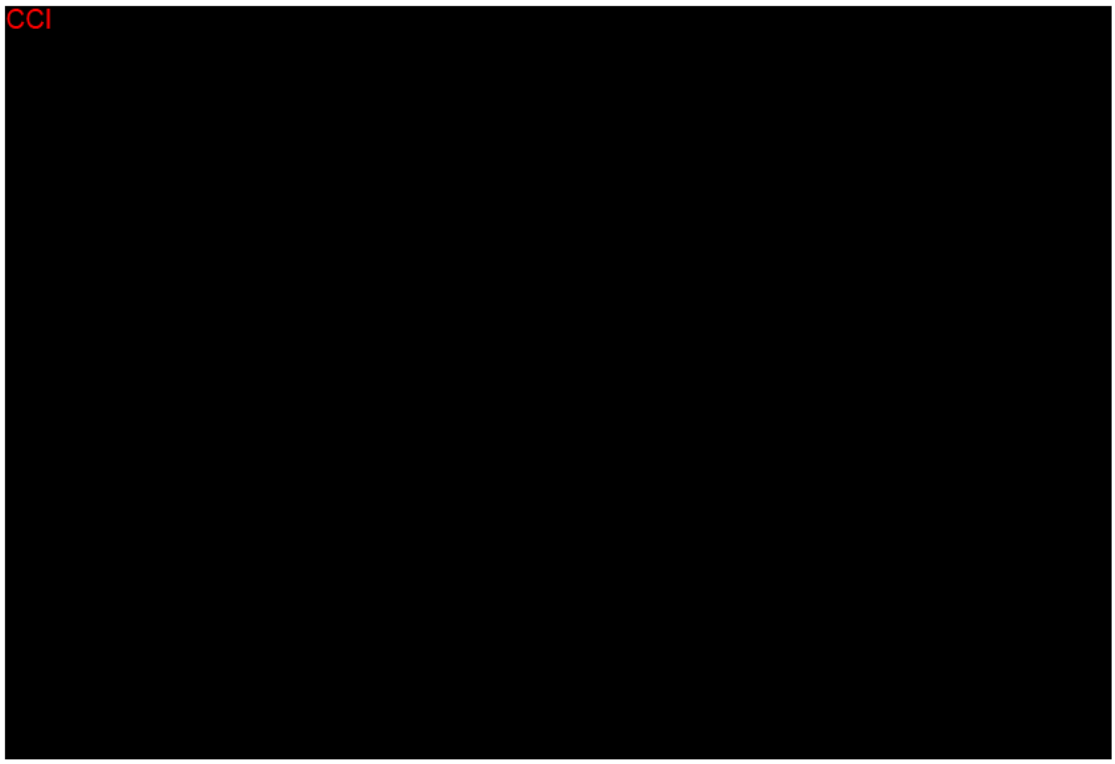
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BTK	Bruton tyrosine kinase
CBCL	Cutaneous B-cell lymphoma
CFB	Change from Baseline
CLL	Chronic lymphocytic leukemia
CR	Complete Response
CRi	Complete Response with Incomplete Marrow Recovery
CRF	Case report form
CTMS	Clinical trial management system
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
DEAS	DLT evaluable analysis set
DD	Drug Dictionary
DLT	Dose limiting toxicity
DMC	Data monitoring committee
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
ENR	All patients enrolled set
FAS	Full analysis set
FL	Follicular lymphoma
IA	Interim analysis
INR	International normalized ratio
IPI	International prognostic Index
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LPL/WM	Lymphoplasmacytic lymphoma / waldenström's macroglobulinemia
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities

MR	Minor response
MRI	Magnetic resonance image
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
MZL	Marginal zone lymphoma
NCI	National cancer institute
NA	Not applicable
ND	Not done
NE	Not evaluable
nPR	Nodular partial response
ORR	Objective response rate
PCFB	Percentage Change from Baseline
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PSAS	Pharmacokinetics Analysis Set
PR	Partial response
PR-L	Partial Response with Lymphocytosis
PT	Prothrombin time
PTCL	Peripheral T-cell Lymphoma
QD	Once daily
QTc	Corrected QT interval
RES	Response Evaluable Set
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SLL	Small lymphocytic lymphoma
SRC	Safety review committee
TEAE	Treatment emergent adverse events
TESAE	Treatment emergent serious adverse events
TTR	Time to response
ULN	Upper limit of normal
VGPR	Very good partial response
WHO	World health organization

Note: Standard units such as mg and mL as used in the text are not included in the abbreviations list.

2. INTRODUCTION

This study is a two-stage, open-label, multicenter Phase 1 study to evaluate the safety, Pharmacokinetics (PK), and preliminary efficacy of HMPL-523 in patients with relapsed or refractory lymphoma who have exhausted approved therapy options. The study consists of two stages. Stage 1 is a dose escalation phase, in which a modified 3+3 design is applied for the dose escalation and to determinate the maximum tolerated dose (MTD) / recommended Phase II dose (RP2D). Stage 2 is a dose expansion stage, in which the safety, tolerability, PK, and preliminary efficacy of HMPL-523 at MTD/RP2D will be further evaluated in patients with relapsed, refractory, or resistant NHL.

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods and conventions to be implemented in the presentation and analysis of efficacy and safety data from study 2018-523-00US1. This document is based on Protocol Amendment 5 dated 14Jun2024. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. If circumstances arise during the study such that more appropriate analytic procedures become available, the SAP may be revised. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be identified. Any revisions to the SAP will be made and finalized prior to the final Database Lock (DBL), and any deviations from the SAP will be documented in the final Clinical Study Report (CSR).

The PK and pharmacodynamics analyses will be described in a separate analysis plan. All statistical analyses except for PK specific analyses will be performed by IQVIA Biostatistics.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objectives are:

- To evaluate the safety and tolerability of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation stage.
- To determine MTD/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.

3.2. SECONDARY OBJECTIVES

The secondary objectives are:

- 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

The exploratory objectives are:

- To evaluate the PK properties of the major metabolites of 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 anti-tumor activities of HMPL-523.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

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.

As of CCI [redacted] 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.

4.1.1. DOSE ESCALATION STAGE (STAGE 1)

In the dose escalation stage (Stage 1), a modified 3+3 design will be applied for dose escalation and MTD/RP2D determination, starting dosing from 100 mg QD orally. A cycle of study treatment will be defined as 28 days of continuous dosing.
For all patients in Stage 1, DLTs will be assessed during the DLT assessment window of 28 days (i.e., from Cycle 1 Day 1 [the day of first administration of treatment] through Cycle 1 Day 28). 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.

The sample size for Stage 1 is based on the dose-escalation rules of the 3+3 design. The proposed dose escalation cohort include 6 groups: 100mg QD, 200 mg QD, 400 mg QD, 600 mg QD, 700 mg QD, and 800 mg QD.

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

To enhance the safety and integrity of the study, a Safety Review Committee (SRC) 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 will convene to review all accumulated data for the study. The SRC will periodically convene following the completion of each dose level cohort and before enrollment may proceed to the next dose level.

4.1.2. 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.
Upon implementation of protocol amendment 5 and closure to enrolment, a total of 48 patients were enrolled in the dose-expansion portion. The last patient was enrolled on CCI . .

4.2. SAMPLE SIZE DETERMINATION

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

4.2.1. STAGE 1: DOSE ESCALATION STAGE

The sample size for Stage 1 was 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.

4.2.2. STAGE 2: DOSE EXPANSION STAGE

The planned enrollment for Stage 2 was approximately 70 patients. The anticipated enrolment of 70 patients was to provide more robust safety data in the patient populations studied. For a given AE with a true incidence 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.

4.3. SCHEDULE OF EVENTS

Schedule of events can be found in APPENDIX 1 of the protocol.

5. PLANNED ANALYSES

A soft lock for a data snapshot was performed followed by a preliminary evaluation of selected efficacy and safety endpoints to support a publication.

5.1. INTERIM ANALYSIS (IA)

There was no planned IA for this study, however, additional analyses may have been conducted upon sponsor request for internal decision-making purposes, for example to provide information for a potential Phase 3 study design.

5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics by following sponsor's authorization of this SAP prior to DBL for this study.

6. ANALYSIS SETS

6.1. ALL PATIENTS ENROLLED SET [ENR]

The ENR will contain all patients who provided informed consent for this study.

6.2. FULL ANALYSIS SET [FAS]

The FAS is defined as all patients who received at least 1 dose of HMPL-523. The FAS will be used for the analysis of safety data and efficacy data (except Objective Response Rate [ORR], Time to Response [TTR], and Duration of Response [DoR]). Patients will be analyzed by their actual dose initially received. If patients were dose reduced during the study, all data will be summarized/analyzed based on the initial dose of study treatment received.

6.3. RESPONSE EVALUABLE SET[RES]

The RES is defined as all patients who received at least 1 dose of HMPL-523, have a baseline tumor measurement, and have at least 1 post-baseline tumor measurement or clinical restaging, unless death occurs before the first post-baseline assessment. The RES will be the primary population for the analysis of ORR, TTR, and DoR.

6.4. DLT Evaluable Analysis Set (DEAS)

The DLT Evaluable Analysis Set (DEAS) is defined as all patients who have received at least 75% of the assigned dose of study treatment during the DLT assessment window of 28 days (ie, from Cycle 1, Day 1 [the day of the first administration of treatment] through Cycle 1, Day 28) in Stage 1 or have not completed the DLT assessment period due to a DLT.

6.5. 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. General Considerations

7.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of first administration of treatment and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date, then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day, and any corresponding durations, will be presented based on the imputations specified in section 7.8: Handling of Missing Data.

7.2. Baseline and Change from Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the day of first administration of treatment (including unscheduled assessments). Bone marrow biopsy and/or aspirate were done at baseline or up to 3 months before of the Cycle 1 Day 1. In the case where the last non-missing measurement is taken on the day of first administration of treatment without time point collected, that measurement will be considered baseline. For

Electrocardiogram (ECG) parameters, last assessment performed prior to or on first dose date with time point marked as "pre-dose" will be considered as baseline. For those patients without pre-dose ECG record at date of the first dose, the last non-missing measurement taken prior to the day of first administration of treatment will be treated as baseline. Adverse Events (AEs) and medications commencing on the day of first administration of treatment will be considered post-baseline.

For quantitative measurements, change from baseline (CFB) will be calculated as:

- CFB = Assessment value at each visit – Baseline value.

Percentage CFB (% CFB) will be calculated as:

- % CFB = (Assessment value at each visit – Baseline value)/Baseline value × 100.

7.3. On Treatment Period and Worst Post-Baseline

For the analysis purpose, on treatment period is defined as the period from the day of first dose of treatment to 37 days after the last dose of treatment or the initiation of new antineoplastic therapy, whichever comes earlier.

The severity of adverse events and laboratory results depends on CTCAE grade. The worst post baseline value is defined as the highest CTCAE grade during on treatment period.
The worst post-baseline abnormality is defined in the order of Abnormal, Clinically Significant>Abnormal, Not Clinically Significant>Normal during the on-treatment period.

7.4. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/ worst case value where required (e.g. shift table).

In the case of a retest (visit-specific unscheduled visit number assigned), the latest non-missing measurement among all scheduled and unscheduled measurements for that visit will be used for by-visit summaries.
For ECG triplicate records, the mean value will be used for by visit summaries.
Early termination data of patients prematurely discontinued from study medication will be presented together with the end of treatment assessment for study medication completers.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.5. SUBGROUPS

Not applicable.

7.6. WINDOWING CONVENTIONS

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle defined as Day 1, to the dates that the scheduled visits occurred. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in **Error! Reference source not found.**. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient's listings. For windowed visits during the treatment cycles, if more than one visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used.

Error! Reference source not found.**: Visit Window**

	Cycle 1				Cycle 2		Cycle 3 and onwards	Last Cycle	Follow-up	
	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±3)	D1 (±3)	CXD1	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
Scheduled Day [a]	1	8	15	22	1	15	1	1		
ECOG performance status	Day1		2 to EOC -3		Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC	Last dose date of last cycle +1 to last dose date of last cycle +37	
Vital signs	Day1	2 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC		

	Cycle 1				Cycle 2		Cycle 3 and onwards	Last Cycle	Follow-up	
	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±3)	D1 (±3)	CXD1	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
Hematology		1 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC		
Urinalysis/ dipstick			1 to EOC -3		Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC		
Chemistry panel		1 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC		
Beta 2-microglobulin					Cycle 1 Day 1 to EOC -3		Day -3 to EOC-3	Day-3 to EOC		
Fasting lipid profile					Cycle 1 Day 1 to EOC -3		Day -3 to EOC-3	Day-3 to EOC		
Serum amylase and lipase		1 to 11	12 to 18	19 to EOC-3	Day -3 to 8	9 to EOC -3	Day -3 to EOC-3	Day-3 to EOC		
Coagulation assay (INR, aPTT, PT)					Cycle 1 Day 1 to EOC - 3		Day -3 to EOC-3	Day-3 to EOC		
Leukocyte immunophenotyping			1 to EOC -3		Day -3 to EOC -3		Day -3 to EOC-3	Day-3 to EOC		
Echocardiogram/MUGA										

	Cycle 1				Cycle 2		Cycle 3 and onwards	Last Cycle	Follow-up	
	D1	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±3)	D1 (±3)	CXD1	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
12-Lead ECG	Day 1-2		3 to EOC -3		Day -3 to EOC -3		Day -3 to EOC-3	Day-3 to EOC		
Quantitative serum immunoglobulin levels (for WM/LPL)					Cycle 1 Day 1 to EOC -3		Day -3 to EOC-3	Day-3 to EOC		X
CT/PET-CT							Cycle 1 Day 1 to EOC-3	Day-3 to EOC		X

[a] The scheduled day is relative to Day 1 of each cycle.
Note: The end date of a cycle (EOC) is defined as one day earlier than the date of Day 1 study drug administration of its next cycle. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as the last dose of the last cycle.
EOC = end of cycle.

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS® version 9.4 or higher.

7.8. DATA HANDLING CONVENTIONS

Data will be summarized by dose level (Stage 1), malignancy type (Stage 2), and overall as appropriate. Some summary results (efficacy) for Stage 1 may be also presented by malignancy type (e.g., for any interim looks).

Continuous assessments will be summarized by number of patients (n), mean, standard deviation, median, minimum, and maximum. The decimal places for minimum and maximum will be the same as the max decimal places in original data. Mean and Median will keep one

more decimal place than the decimal places in original data; standard deviation will keep 2 more decimal places than the decimal places in original data, but no more than 4 decimal places.
For categorical variables, descriptive statistics will include the number and percentage of patients for each category. The denominator for all percentages will be the number of patients in that treatment group or malignancy type within the population of interest, unless otherwise noted. The percentage will keep one decimal places. If the percentage is 100%, 100% will be reported; if the frequency is 0, no percentage will be reported. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30, not .12 – .30).
If needed, the 2-sided 95% confidence interval for percentage will be calculated using Clopper-Pearson method (Clopper, C. J., & Pearson, E. S. 1934) as well, and the decimal places will be the same as percentage.

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

7.9. MISSING DATA

In general, all available data will be included in the analyses. Unless otherwise specified, there will be no substitution of missing data, i.e. missing data will not be replaced but will be handled as 'missing' in the statistical evaluation. Partial dates may be imputed for statistical analyses for specific outcomes. In such cases, the specific imputation rules are provided below. However, as a global convention, imputed dates should not be shown in listings.

Adverse Events
If the adverse event onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication. Adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study medication or more than 30 days after last dose of study medication or new antineoplastic therapy.

Missing or partial start dates:

- If the date has no missing year and month but the day is missing:
  - 1) If the year and month of first dose date are the same as the year and month of the start date, then the date of first dose will be used.
  - 2) Otherwise, 1st day of the month will be used.
- If the date has no missing year, but has missing month, and the year of first dose date is the same as the year of the start date, the date of first dose will be used.
- If the date has no missing year, but has missing month, and the year of first dose is

not the same as the year of the start date, then January 1st will be used.
- If the start date is completely unknown, then use the date of first dose.

Missing or partial stop dates:

- If the date has no missing year and month but the day is missing, then use the last day of the month.
- If the date has no missing year, but has missing month, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date.

Note: For patients who died, if the imputed start/stop date is later than date of death, the imputed date will set to be date of death.

Concomitant Medications/Procedures

If concomitant medication start and/or stop dates are missing or partial date, the dates will be compared as far as possible with the date of first dose of study medication.
Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be prior.

Missing or partial start dates:

- If the date has no missing year and month but the day is missing, the 1st day of the month will be used.
- If the date has no missing year, but has missing month, then January 1st will be used.
- If the start date is completely unknown, do not impute the start date.

Missing or partial stop dates:

- If the date has no missing year and month but the day is missing, then use the last day of the month.
- If the date has no missing year, but has missing month, then use December 31st of that year.
- If the stop date is completely unknown, do not impute the stop date, and assign

'ongoing' status.

Note: For patients who died, if the imputed start/stop date is later than date of death, the imputed date will set to be date of death.

Death Date

- If year and month of death date are known but the day is unknown, day will be imputed as 15 (for example, if a patient is reported to die on December 2017, the death date will be imputed as 15 December 2017).
- If only year are known, death date will be imputed as 1st July of the given year.
- If the imputed death date is prior to the last known alive date, then the death date will be imputed as last known alive date+1.
- If death date is totally missing, dates will be imputed as the last known alive date + 1.
- Last known alive date could be derived from the latest date from:

  Adverse event start/stop dates
  Concomitant medication start/stop dates
  Concomitant procedure start/stop dates
  Subsequent therapies start dates
  HMPL-523 treatment start/end dates
  Tumor scan dates
  PET-CT examination dates
  Laboratory sample collection dates
  ECG dates
  Vital signs assessment dates
  ECOG assessment dates
  Physical examination dates
  ECHO assessment dates
  End of Treatment date
  End of Study date (exclude lost to follow up reason)

Note: if the imputed death date is after the end of study date, then the death date will be imputed as the end of study date.

Last dose date

Missing or partial date of last dose date of study treatment:

- If the date is partially missing, then impute the date as the last day of given part of original last dose date. If the day is missing, imputed date will be the last day of the month of the partial last dose. If the month is missing, imputed date will be the last

day of the year of the partial last dose. If the imputed date is after the end of study date, then it will be replaced with the end of study date.

- If the date is completely missing, then impute the date at end of study date.

Subsequent anti-cancer therapy

Missing or partial start date of anti-cancer therapy after end of study treatment:

- If the date has no missing year and month but the day is missing and if the date has same year and month with last dose date, then equal to last dose date+1, else 15th day of the month will be used.
- If the date has no missing year, but has missing month, and the year of last dose date is the same as the year of the start date, the date of last dose+1 will be used.
- If the date has no missing year, but has missing month, and the year of last dose is before the year of the start date, then July 1st will be used.
- If the start date is completely unknown, then use the date of last dose+1.

Birth Date

Missing or partial birth date:

- If only year is present, July 1st will be used to impute the birth date.
- If only year and month is present, 15 will be used to impute the birth date.

Oncology Diagnosis History Dates

- If year is missing, do not impute.
- if year and month are known but the day is unknown, day will be imputed as 15.
- If only year is known, month and day would be imputed as July 1st.

Note: The imputed date will be compared to inform consent date. If it is later than the inform consent date, the incomplete date will be imputed as the inform consent date.

8. OUTPUT PRESENTATIONS

Summary results will be presented by Stage 1 and Stage 2. For Stage 1, summary will be by dose level. For Stage 2, summary will be by type of malignancies and overall. Some of the efficacy summary results for Stage 1 may be presented by type of malignancy for any interim looks.

9. DISPOSITION AND WITHDRAWALS

All patients who provided informed consent will be accounted for in this study.

9.1. DISPOSITION

Patient disposition, discontinuation as well as reasons for discontinuation will be presented for the all enrolled set. The number of patients who provided informed consent for the study will be summarized. Screen failed patients and the reason for screen failure as well as patients who passed screening but withdrew before study treatment will also be summarized.
The number and percentage of patients who completed, discontinued or were still on the treatment will be presented. Reasons for discontinuation from study treatment as recorded on the "End of Treatment (EOT)" form will be summarized. The number and percentage of patients who have completed, discontinued or were still on study will be presented. Reasons for discontinuation from study as recorded on "End of Study (EOS)" form will be summarized. The follow up time will be also summarized with mean, median, and standard deviation.
Follow up time (days) = the latest date in database – the first dose date + 1. For the interim evaluation of Stage 1 results, follow-up time (days) is defined as date of cutoff (even if patient was off treatment or died after the cutoff date) – first dose date +1.
In addition, number and percentage of patients with <6, >=6, <12, >=12 months follow-up time will be summarized.

The number/percentage of patients included in FAS, RES, DEAS (stage 1 only), and PKAS will be summarized for both Stage 1 and Stage 2. A by-patient listing will include the inclusion/exclusion of patients in each analysis set.

Individual listings containing the site and patient number, informed consent information, first and last study medication administration date, treatment discontinuation information and end of study information will be provided separately for Stage 1 and Stage 2. A separate data listing will include eligibility for study entry based on inclusion/exclusion criteria.

9.2. PROTOCOL DEVIATIONS

Protocol deviations will be collected by the clinical team and entered into the clinical trial management system (CTMS). The study team will discuss, identify and classify the important eligibility criteria or post-entry deviations from operational team monitor reports before final data base lock. A summary table for protocol deviations by major deviation category will be presented. Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient

management, or patient assessment will be also listed for FAS. The protocol deviation listing will present deviation category, deviation term, deviation date, severity (major/minor), and actions taken.

COVID-19 Visit Impact to planned visit will be included in by-patient listings.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and other baseline characteristics will be presented for the FAS.
Continuous demographic variables: age, height, weight, and body mass index will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). For all the other categorical variables, results will be presented as number and percentage of patients.
The following demographic and baseline characteristics will be reported for this study:

- Age (years) = floor ((date of informed consent-date of birth+1)/365.25
- Age Category:
    - <65 years
    - >=65 years
- Gender (including childbearing potential for female patients)
- Race
- Ethnicity
- Weight at Baseline (kg)
- Height at Baseline (cm)
- BMI (kg/m2) at Baseline = weight(kg) *10000/(height(m)*height(m))
- Alcohol Use
- Drug Abuse
- Tobacco Use
- Baseline Eastern Cooperative Oncology Group (ECOG) Performance Status
    - 0
    - 1
    - >1
- Baseline LVEF (%)
- Initial Tumor Type (CLL, SLL, MCL, FL, WM/LPL, MZL, PTCL, CBCL, DLBCL) and sub-

types for MZL, and PTCL, and prior BTK inhibitor exposure for CLL/SLL only.

- B-symptoms
    - Unexplained weight loss >= 10% over previous 6 months (Yes, No, Unknown)
    - Fever > 38 C/100.5 F for 2 or more weeks without other evidence of infection (Yes, No, Unknown)
    - Night sweats for more than 1 month without evidence of infection (Yes, No, Unknown)
- Bone Marrow Involvement by PET-CT
- Bone Marrow by Biopsy
- Bone Marrow by Aspirate
- Serum Beta 2-Microglobulin
- Viral Serology
- Serum Immunoglobulin
- Leukocyte Immunophenotyping
- 17p del/TP53 Mutation Status

11. OTHER BASELINE DISEASE CHARACTERISTICS

Prior cancer diagnosis includes tumor type, immunohistochemistry, flow cytometry, other pathological findings, prior anti-neoplastic therapies and procedures and related outcome.
FAS will be used to summarize baseline disease characteristics. Results will be displayed by dose level for stage 1 and by types of malignancy for stage 2.
The disease related baseline characteristics will be summarized by the type of malignancy as following:

- Time since diagnosis (months) calculated as (date of first dose date – date of primary diagnosis + 1)/30.4375
    - Initial Immunohistochemistry, Flow Cytometry and other Pathological Findings
    - Rai stage (only for patients with lymphoma type CLL)
    - Binet stage (only for patients with lymphoma type CLL)
- Ann Arbor Staging at study entry (for patients with lymphoma other than CLL)
- Risk Groups
    - For CLL/SLL/MZL: Low, Low-intermediate, High-Intermediate, High from "Diffuse Lymphoma International Prognostic Index" CRF page
    - For FL: Low, Intermediate, High from "Follicular Lymphoma International

Prognostic Index" CRF page
- For MCL: Low, Intermediate, High from "Simplified Mantel Cell Lymphoma International Prognostic Index (MIPI) Score" CRF page
- For WM/LPL: Low, Intermediate, High from "International Prognostic Scoring System for Waldenstrom's Macroglobulinemia (ISSWM)" CRF page

12. PRIOR ANTI-CANCER THERAPY

Prior oncology therapy will be summarized for the FAS. Prior oncology therapies are defined as any anti-cancer therapy stopped before 3 weeks prior to initiation of study treatment.
Prior oncology therapies include prior oncology chemotherapy and oncology medication, prior oncology radiotherapies and prior oncology surgeries/procedures.
Prior oncology medications will be coded using World Health Organisation Drug Dictionary Enhanced (WHO-DDE) version SEPT 2024. Medications will be presented by Anatomical Therapeutic Chemical (ATC) level 2 text and preferred term (PT). ATC class and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, ATCs/PTs will be presented alphabetically for ATCs/PTs of the same total frequency.
Prior oncology surgeries/procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1 and presented with system organ class (SOC) and PT in a listing.
Radiotherapies are not considered a line of prior oncology therapy. Radiotherapies will be listed in the listing of prior therapies.
Prior oncology medication therapies will be summarized with the following items:

- Number and percentage of patients with at least one prior oncology medication therapy
- Number and percentage of patients with 1, 2, 3, and >3 previous lines of therapy
- Number of max regimens of prior oncology medication therapy
- Time since last oncology medication therapy (month) = (date of first dose – last date for the last therapy + 1)/ 30.4375
- Best response for last oncology medication therapy

13. MEDICAL HISTORY

Medical History information will be presented for the FAS.

All medical history from eCRF page 'Medical History' will be coded with MedDRA Version 27.1 and summarized by SOC and PT. Number and percentage of patients will be presented in frequency tables, ordered by primary SOC and PT in descending order of the frequency in total group. For SOCs or PTs with the same frequency, categories will be sorted alphabetically.

14. CONCOMITANT MEDICATIONS AND PROCEDURES

14.1. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be presented for the FAS and will be coded using WHO-DDE version SEPT 2024.

Refer to Section 7.9 for handling of missing or partial dates. In the case where it is not possible to define a medication as prior or concomitant based on dates, the medication will be classified as concomitant.

'Prior' medications are medications which started and stopped prior to the day of the first administration.

'Concomitant' medications are those which:

- Started prior to the first administration date of study medication and ended on or after the first administration date on treatment.
- Started on or after the first administration date of study medication but no later than 37 days following last administration date on treatment or start of a new treatment of anti-neoplasm therapy, whichever is earlier.

Prior and concomitant medications will be presented by ATC level 2 text and PT. ATC class and PT will be sorted in descending frequency of the total number of patients with at least one condition in the corresponding category, ATCs/PTs will be presented alphabetically for ATCs/PTs of the same total frequency.

14.2. CONCOMITANT PROCEDURES

Concomitant procedures are defined as procedures that occurred at any time on or after the day of the first administration and no later than 37 days following the last administration date on treatment of study medication or start of a new treatment of anti-neoplasm therapy, whichever is earlier. Procedures will be presented for the FAS and will be coded using MedDRA Version 27.1 or higher. Concomitant procedures will be summarized and listed by SOC and PT. Number of patients and percentage in the analysis set will be presented in frequency tables, ordered by

primary SOC and PT in descending order of the frequency in total group. For SOCs or PTs with the same frequency, categories will be sorted alphabetically.

14.3. SUBSEQUENT MEDICATIONS AND NON-DRUG TREATMENTS

Subsequent oncology therapy is defined as any new anti-neoplastic therapy (including medication, surgery/procedure, and radiotherapy) started after last dose of study medication. Subsequent oncology therapy will be summarized and listed for the FAS.

15. STUDY MEDICATION EXPOSURE AND COMPLIANCE

Exposure to study medication in days will be summarized based on the FAS.
The date of first study medication administration will be taken from the "HMPL-523 Treatment" eCRF form. The date of last study medication will be taken from the last study medication administration date.
Study drug interruptions, compliance, and dose changes are not taken into account for duration of exposure.
The following study medication administration summaries will be reported for this study:

- Number of cycles: the number of cycles in which the patient took any dose of study medication.
- Total duration exposure (months):

$$\text{Total duration of treatment (months)} = \left(\frac{\text{date of last dose - date of first dose+1}}{30.4375}\right)$$

It will be summarized as continuous variables and also categorized into groups as below:

- < 6 months exposure
- >=6 to < 12 months exposure
- >= 12 months exposure

- Actual duration of study treatment (months):

Actual duration of study treatment is defined as the total number of months on the study medication during the treatment phase (excluding the periods of dose discontinuation or dose interruptions).

- Cumulative dose (mg):

Cumulative dose (mg) is defined as the sum of the total doses patient actually received during an exposure period.

- Dose intensity (mg/day):

$$\text{Dose intensity (mg/day)} = \left(\frac{\text{Cumulative dose (mg)}}{\text{total treatment exposure(days)}}\right)$$

- Relative dose intensity (%):

$$\text{Relative dose intensity (\%)} = \left(\frac{\text{dose intensity (mg/day)}}{\text{planned dose intensity(mg/day)}}\right) * 100$$

The planned dose intensity is defined in the protocol for each cohort:100mg/day, 200mg/day, 400 mg/day, 600 mg/day, 700 mg/day, and 800 mg/day.

It will be summarized as continuous variables and also categorized into groups as below:

- < 50%
- 50% - <70%
- 70% - <90%
- 90% - <110%
- >=110%

The number and percentage of patients with any dose modification will be presented. Dose modification will be further characterized by presenting the numbers and percentages of patients with any dose reduction, dose escalation and dose interruption. Reasons for dose adjustments will be summarized as well.

Details of study treatment administration will be included in patient listings.

16. EFFICACY OUTCOMES

Tumor assessment will be conducted every 8 weeks (±7 days) for the first 24 weeks and then every 12 weeks (±7 days) thereafter.
Efficacy analysis will be performed using the RES for ORR, TTR, and DoR endpoints and using the FAS for the PFS endpoint.
Unless otherwise specified, all efficacy outputs are to be summarized by dose cohort for Stage 1 and by type of malignancy in Stage 2.

16.1. EFFICACY PARAMETERS

16.1.1. EFFICACY PARAMETERS & DERIVATIONS

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

- CLL: modified IWCLL 2008
- WM/LPL: IWWM-7
- SLL, MCL, FL, MZL, PTCL, CBCL, DBLCL: Lugano Response Criteria for Non-Hodgkin's Lymphoma (Cheson et al 2014)

Best overall response (BOR)
The best overall response (BOR) for 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.

Best overall response is determined from the sequence of responses assessed as below:

- For CLL guideline: Complete Response (CR), CR with incomplete bone marrow recovery (CRi), Partial Response (PR), Nodular Partial Response (nPR), Partial Response with Lymphocytosis (PR-L), Stable Disease (SD), Progressive Disease (PD), Not all evaluated (NE).
- For WM guideline: Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minor Response (MR), Stable Disease (SD), Progressive Disease (PD), Not Evaluated (NE).
- For Other Lymphomas guideline: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluated (NE).

For patients with multiple assessment for same visit, the earliest date will be selected for PD, while the latest date will be selected for other response.

Patients with BOR "NE" will be summarized by reason for having NE status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response NE

Patients with a BOR of "Unknown" or "NE" will be considered non-responders in estimating response rates.

The number and percentage of patients with BOR of CR, CRi, VGPR, PR, nPR, MR, PR-L, SD, PD, and NE will be summarized by dose level and overall in Stage 1, by the malignancy type and overall in Stage 2.

Objective response rate (ORR)

ORR is defined as the proportion of patients who have BOR with CR, CRi, nPR or PR for CLL patients; the proportion of patients who have BOR with CR, VGPR, PR or MR for WM patients; the proportion of patients who have BOR with CR or PR for patients with disease type other than CLL and WM.
The definition of neo-OR is similar with that of classical OR except that partial response with lymphocytosis (PR-L) is also included for CLL.
The estimated ORR and 95% Clopper-Pearson CI (Clopper, C. J., & Pearson, E. S. 1934) will be presented by dose level for Stage 1 and by the malignancy type for Stage 1 and Stage 2.

Complete Response Rate (CR rate)

CR rate is defined as the proportion of patients who have BOR with CR or CRi for CLL patients, and CR only for other patients.
The estimated CR rate and 95% Clopper-Pearson confidence interval (CI) (Clopper, C. J., & Pearson, E. S. 1934) will be presented by dose level for Stage 1 and by the malignancy type for Stage 2.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients who have BOR of stable disease (SD) or better.
The clinical benefit for each type of malignancy is defined as following:

- CLL: BOR with CR, CRi, nPR, PR, PR-L or SD
- WM: BOR, with CR, VGPR, PR or SD, MR
- Other types of disease: CR, PR or SD

The estimated CBR and the corresponding 95% exact CI using Clopper-Pearson method (Clopper, C. J., & Pearson, E. S. 1934) will be summarized for presented by dose level in Stage 1 and type of the malignancy for Stage 2.
CBR data will be listed for all patients in RES.

Progression free survival (PFS)

PFS is defined as the time (in months) from the date of first study medication to the earliest date of disease progression or death due to any reason whichever occurs first.

PFS (months) = ([date of progression or death or censoring] - [date of first dose of study medication] + 1)/30.4375.
A patient is deemed to be censored according to the rules specified in **Error! Reference source not found.** below.

Error! Reference source not found.**: Progression-Free Survival Censoring Rules**

#	Situation	Date of Progression or Censoring	Outcome	Event/Censor reason
1	Death (without previously documented progressive disease [PD]) within two evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment)	Date of death	Event	Death
2	Death (without previously documented PD) after two or more consecutive missed/non-evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment)	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment)	Censored	Death after two or more consecutive missed or NE tumor assessments
3	Progression within two evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment before PD)	Date of progression	Event	Disease Progression
4	Progression after two or more consecutive missed/non-evaluable tumor assessments[a] from last evaluable tumor assessment or first dose (if no post-baseline tumor assessment before PD)	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment before PD)	Censored	Progression after two or more consecutive missed or NE tumor assessments
5	Progression after new anti-cancer treatment	Date of last evaluable tumor assessment before new anti-cancer treatment or date of first dose (if no post-baseline tumor assessment before new anti-cancer)	Censored	Progression after new anti-cancer therapy
6	No baseline tumor evaluable assessment and alive	Date of first dose	Censored	No baseline assessment
7	No post-baseline tumor evaluable assessment and alive	Date of first dose	Censored	No post-baseline assessment

8	New anti-cancer treatment started with no progression[b]/death	Date of last evaluable tumor assessment before new anti-cancer treatment or date of first dose (if no post-baseline tumor assessment before new anti-cancer)	Censored	Initiation of new anti-cancer therapy without PD/death observed
9	No disease progression or death	Date of last evaluable tumor assessment or date of first dose (if no post-baseline tumor assessment)	Censored	Progression free at time of analysis: the patient is known to be alive without any progression happened at the end of study date

[a] time period that identifies two consecutive missed/non-evaluable tumor assessments is calculated as 2*(the planned duration between assessments + protocol allowed visit window) from the last evaluable tumor assessment or date of first dose (if no post-baseline evaluable tumor assessment). According to protocol, tumor assessment will be conducted every 8 weeks for the first 24 weeks and every 12 weeks thereafter (±7 days). Additional details are provided below.
[b] See algorithm below

Given the schedule of visit assessments, the definition of two missed consecutive tumor assessment visit may vary; please refer to following rules:

- If the last evaluable tumor assessment before PD/death is less than 120 days (week 16 which is 8 weeks before week 25, and allowing for 7 days for late visit, hence 7*16 weeks + 7 days for a late visit + 1 day*=120 days) then two consecutive assessments equates to 126 days since last evaluable tumor assessment, allowing for early and late visits (2*8 weeks + 7 days for an early assessment + 7 days for a late assessment).

  *Note the 1 day comes from study days = date of tumor assessment – date of first dose + 1 day.
- If the two missed assessments occur over the period when the scheduled frequency of tumor assessments change from 8-weekly to 12-weekly, which means last evaluable tumor assessment is from week 16 to 25 (days 120 to 176), then two consecutive assessments equates to 154 days (7*8 weeks + 7*12 weeks + 7 days for an early assessment + 7 days for a late assessment).
- From day 176 (week 25) onwards (when the scheduling changes to 12-weekly assessments). two missing consecutive assessments equates to 182 days (2*12 weeks + 7 days for an early assessment + 7 days for a late assessment).

  [b] for patients who receive new anti-cancer therapy, the following rules will apply:
- If the start date of new anti-cancer therapy is completely missing, then impute the date as

last dose of study treatment + 1.

- If the start date of new anti-cancer therapy is partial, the imputation rules refer to section 7.9.
- If new anti-cancer therapy is started without PD or is started prior to PD or death, the PFS will be censored at the date of the last evaluable tumor assessment no later than the date of initiation of new anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy, the assessment will be used as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy).
- If a patient has only a baseline visit or does not have an assessment that is no later than the date of initiation of new anti-cancer therapy, the PFS will be censored at the date of first dose.

The median and quartiles for PFS and the PFS rates at 6 months, 12 months, together with their two-sided 95% confidence intervals will be estimated for each dose level (Stage 1) and malignancy type (Stage2) using the Kaplan-Meier method. The 95% CI for the median will be calculated from a log-log transformation based on the method by Brookmeyer and Crowley (Brookmeyer, R., & Crowley, J. 1982). Kaplan-Meier curves will be plotted.

Frequency and percentage for each type of event (PD or death) and censoring reasons will be presented as categories.
The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Duration of response (DoR)

Duration of response (DoR) is defined as the time from when the first response (CR, CRi, PR. nPR, VGPR, PR-L, and MR) was achieved until the earlier of the first documentation of definitive disease progression or death from any cause. If patients do not have disease progression or death, they will be censored following the same rules as for PFS. Only patients with response of CR, CRi, PR, nPR, VGPR, PR-L, or MR will be included in the analysis for DoR.

DoR (months) = ([date of first documentation of definitive PD or death from any cause] - [date of first response] + 1)/30.4375.

Percentages for the number of events/censorings of DoR will be calculated based on the number of responders.

Median DoR along with the two-sided 95% CI will be estimated using Kaplan-Meier method. The 95% CI for the median will be calculated using a log-log transformation based on

Brookmeyer and Crowley (Brookmeyer, R., & Crowley, J. 1982) method. Kaplan-Meier curve will be plotted by dose level in Stage 1 and by the malignancy type in Stage 2.

Time to response (TTR)

TTR is defined as the time from the first dose of study treatment to the first occurrence of CR, CRi, PR, nPR, VGPR, PR-L, or MR. Only patient with response of CR, Cri, PR, nPR, VGPR, PR-L, or MR will be included in the analysis for TTR.

TTR = ([date of first response] – [date of first dose of study medication] + 1)/30.4375.
Median TTR along with the two-sided 95% CI will be estimated using Kaplan-Meier method. The 95% CI for the median will be calculated using a log-log transformation based on Brookmeyer and Crowley (Brookmeyer, R., & Crowley, J. 1982) method. Kaplan-Meier curve will be plotted by dose level in Stage 1 and by the malignancy type in Stage 2.

Tumor Burden

Tumor burden is defined as the sum of the product of diameters of all target measurable lesions at each tumor assessment visit.
The best percent change from baseline in tumor burden is calculated as:
(The minimum tumor burden among post-baseline assessments – Baseline tumor burden value)/Baseline tumor burden value × 100
Tumor burden will be missing for that assessment visit if there is a missing value of the product of diameters. Thereof a patient will be considered not evaluable for the measure of the best percent change from baseline in tumor burden.

A waterfall plot will be presented for all patients. Different color will be presented to differentiate various dose levels (for Stage 1) and the different type of malignancy in Stage 2.

A listing with the tumor assessments at baseline and each tumor assessment visit will be presented.

The PET-CT Examination will also be listed.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the FAS with the exception of DLT which will be based on DLT evaluable analysis set.

17.1. DLTs

A DLT is a toxicity or AE occurring in the first cycle (28 days), which is attributable to HMPL-523 and meets the criteria defined in the protocol. All DLTs are recorded in the eCRF page of "DLT Assessment". The toxicities or AEs will be graded according to National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
A summary of DTLs in stage 1 will be presented based on DLT Evaluable Set. For each dose level of HMPL-523 and overall, the following will be provided:

- Number of patients enrolled
- Number of patients in DLT Evaluable Set
- Number of patients with a DLT
- Number of DLTs by DLT category SOC and PT

A listing will present all DLTs by subject and dose level. The by-subject DLT data listings will include at a minimum verbatim term, PT, SOC, NCI-CTCAE grade, and relationship to HMPL-523.

17.2. ADVERSE EVENTS

Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the first dose of study medication and no later than 30 days after the date of last study treatment administration or start of a new treatment of anti-neoplasm therapy, whichever is earlier. An exception is that study medication related SAE collected later than 30 days after the last treatment date or start of a new treatment of anti-neoplasm therapy will be treated as TEAEs.

Refer to Section 7.9 for handling of partial dates for AEs. In the case where it is not possible to classify an AE as treatment-emergent or not, the AE will be classified as treatment-emergent.

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

- Any AE
- Any TEAE
- Any TEAE of CTCAE Grade 3 or higher
- Any TEAE of CTCAE Grade 3
- Any TEAE of CTCAE Grade 4
- Any TEAE of CTCAE Grade 5
- Any Treatment Related TEAE
- Any Treatment Related TEAE of CTCAE Grade 3 or higher
- Any Treatment Related TEAE of CTCAE Grade 3

- Any Treatment Related TEAE of CTCAE Grade 4
- Any Treatment Related TEAE of CTCAE Grade 5
- Any Serious TEAE
- Any Serious TEAE of CTCAE Grade 3 or higher
- Any Serious TEAE of CTCAE Grade 3
- Any Serious TEAE of CTCAE Grade 4
- Any Serious TEAE of CTCAE Grade 5
- Any Treatment Related Serious TEAE
- Any Treatment Related Serious TEAE of CTCAE Grade 3 or higher
- Any Treatment Related Serious TEAE of CTCAE Grade 3
- Any Treatment Related Serious TEAE of CTCAE Grade 4
- Any Treatment Related Serious TEAE of CTCAE Grade 5
- Any TEAE Leading to Dose Reduction
- Any TEAE Leading to Drug Interruption
- Any TEAE Leading to Drug Discontinuation
- Any TEAE Leading to Death
- Any TEAE of Special Interest (AESI)

Listings will include the following:

- All AEs
- All SAEs
- AEs leading to Drug Discontinuation
- AEs Leading to Death
- All AESIs

17.2.1. ALL TEAEs

Incidence (frequency and percentage) of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) by dose level for Stage 1 and by type of malignancy for Stage 2. Patients who experience more than one event within the same SOC and PT will be counted only once for that SOC and PT. Patients who experience more than one event within the same SOC but within different PTs will be counted once for that SOC and once for the different unique PT. All TEAEs will be further summarized by maximum severity and by relationship to study medication.

17.2.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "not related" and "related". TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst relationship to study medication will be used in the corresponding relationship summaries.

17.2.3. Severity

Severity of AEs is graded from Grade 1 through 5 according to NCI CTCAE v5.0. The missing severity will be classified as grade 3. If a patient reports multiple TEAEs under the same SOC/PT, the TEAEs with the maximum severity (i.e., maximum grade) will be used in the summary.

17.2.4. TEAEs Leading to Dose Interruption of Study Medication

AEs leading to dose interruption will be identified as those records with a response of "Drug interrupted" to the item "Action taken with Study Treatment" in the eCRF page of "Adverse Events". Frequency and percentage of TEAEs leading to dose interruption by SOC and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SOC.

17.2.5. TEAEs Leading to Dose Reduction of Study Medication

AEs leading to dose reduction will be identified as those records with a response of "Dose reduced" to the item "Action taken with Study Treatment" in the eCRF page of "Adverse Events". Frequency and percentage of TEAEs leading to dose reduction by SOC and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SOC.

17.2.6. TEAEs Leading to Discontinuation of Study Medication

AEs leading to permanent discontinuation will be identified as those records with a response of "Drug permanently discontinued" to the item "Action taken with Study Treatment" in the eCRF page of "Adverse Events". Frequency and percentage of TEAEs leading to treatment discontinuation by SOC and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SOC.

17.2.7. Serious Adverse Events

Treatment-emergent serious adverse events (TESAEs) are those TEAEs which are recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SOC. TEAEs with a missing seriousness to study medication will be regarded as an SAE.

17.2.8. Drug-related Serious Adverse Events

Drug-related serious adverse events (SAEs) are these AEs which are recorded as "Related" and "Serious" on the Adverse Events page of the eCRF. A summary of serious drug-related TEAEs by SOC and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SOC. TEAEs with a missing relationship to study medication will be regarded as related to study medication. TEAEs with a missing seriousness to study medication will be regarded as serious adverse events.

17.2.9. Adverse Events Of Special Interest

AEs of special interest (AESI) will be identified based on the searching strategy listed in Table 3. AESIs will be summarized based on MedDRA 27.1 by referring to the standardized queries in the table below.

Table 3: AESI Categories

TEAE of special interest	Search strategy
Hepatotoxicity	Drug related hepatic disorders - comprehensive search (SMQ Code 20000006 Narrow search). **Sub-SMQ** Liver related investigations, signs and symptoms (SMQ Code 20000008 Narrow search); Cholestasis and jaundice of hepatic origin (SMQ Code 20000009 Narrow search); Hepatitis, non-infectious (SMQ Code 20000010 Narrow search); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ Code 20000013 Narrow search);

TEAE of special interest	Search strategy
	Liver-related coagulation and bleeding disturbances (SMQ Code 20000015 Narrow search).
Infective pneumonia	Infective pneumonia (SMQ Code 20000231 Narrow search).
Interstitial lung disease/Pneumonitis	Interstitial lung disease (SMQ Code 20000042 Narrow search).
Kidney injury	Acute renal failure (SMQ Code 20000003 Broad search).

SMQ = standard MedDRA query.

A summary of AESI's by SMQ and PT will be presented by descending total frequency of SOC and descending total frequency of PT within SMQ.

17.3. DEATHS

If any deaths are recorded on the "Death Details" page of the eCRF, the information will be presented in a summary table by stage 1 (dose level) and stage 2 (malignancy type) and a data listing.

17.4. LABORATORY EVALUATIONS

The following laboratory evaluations will be summarized in tables:

- Chemistry
- Coagulation
- Fasting lipid profile
- Hematology
- Leukocyte immunophenotyping
- Serum immunoglobulin
- Serum amylase and lipase
- Serum β-2 microglobulin
- Urinalysis

The following laboratory evaluations will be listed in listings:

- Chemistry
- Coagulation
- Fasting lipid profile

- Hematology
- Leukocyte immunophenotyping
- Serum immunoglobulin
- Serum amylase and lipase
- Serum β-2 microglobulin
- Urinalysis
- Pregnancy test
- Viral serology

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (LLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Descriptive statistics for all quantitative laboratory evaluations and change from the baseline will be presented in SI units for each visit.

For laboratory parameters graded by NCI CTCAE, version 5.0 (see Appendix 2), changes in CTC grade laboratory data will be summarized as shift table from baseline to worst post-baseline grade. Baseline CTCAE grade is derived from the last laboratory assessment prior to the first administration of study medication, as defined in section 7.2. Worst (maximum) post-baseline CTCAE grade is derived with all measurements from the first dose administration of study medication to no more than 37 days after the last dose of study medication or new anti-cancer therapies, which comes earlier. Otherwise, the shift table will be presented by 'normal', 'abnormal but not clinically significant', 'abnormal and clinically significant'.

All CTCAE Grade 1 or higher abnormalities in laboratory tests will be flagged in the listings.

The incidence of patients with the following abnormal liver function tests (Hy's Law) at any time post baseline will also be summarized:

- ALT or AST >= 3 x ULN and <= 5 x ULN
- ALT or AST > =5 x ULN
- Total bilirubin >= 2 x ULN
- (ALT or AST >= 3 x ULN) and total bilirubin >= 2 x ULN
- (AST or ALT >= 3 x ULN) and total bilirubin >= 2 x ULN and ALP < 2 x ULN

17.5. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.
The following ECG parameters will be reported for this study by dose levels in Stage 1 and by malignancy type in Stage 2:

- PR Interval (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) = QT interval/cube root of RR interval $\frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant
  - Abnormal, Clinically Significant

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements).
- Overall assessment: shift from baseline to worst post-baseline.

All ECG data will be listed.

17.5.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria by visit:

- Absolute values for QTcF will be classified as:
  - > 450 to ⩽480 msec
  - > 480 to ⩽500 msec
  - > 500 msec
- Change from Baseline for QTcF will be classified as:
  - >30 to ⩽60 msec increase from baseline
  - >60 msec increase from baseline
- Absolute values for heart rate will be classified as:
  - <50 bpm
  - >100 bpm
- Absolute values for PR interval will be classified as:
  - interval >200 msec
- Absolute values for QRS interval will be classified as:
  - interval >120 msec

A summary table summarizing the number and percentage of patients with markedly abnormal ECG results will be presented. ECG data will also be presented in a listing.

17.6. VITAL SIGNS

The following Vital Signs measurements will be reported:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (resp/min)
- Temperature (ºC)
- Weight (kg)
- BMI (kg/m^2)

Actual results and change from baseline by visit will be summarized. All vital signs data will be listed.

17.7. PHYSICAL EXAMINATION

The physical examination data will be listed.

17.8. SPLEEN AND LIVER ASSESSMENT

The Spleen and Liver Assessment data will be listed.

17.9. ECOG PERFORMANCE STATUS

The incidence of ECOG performance status will be presented by visit. In addition, ECOG performance status will be presented using shift table to compare baseline to the worst post-baseline value. Values from post-baseline unscheduled visit will be considered when deriving worst post-baseline value.

All ECOG data will be listed.

17.10. ECHOCARDIOGRAM/MUGA

The Echocardiogram/MUGA data will be summarized by visit (descriptive statistics) and listed.

18. 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 and its metabolites versus time data will be tabulated and presented. The individual and mean PK parameters determined following analysis of the concentration of HMPL-523 and its metabolites 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 PK SAP.

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

19. REFERENCES

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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	

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
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		X		
HIV, HBV, and HCV 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										

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
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 plasma sampling[22]			Refer to protocol 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										

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; CLL=chronic lymphocytic leukemia; CR=complete response; CrCl=creatinine clearance; CT=computer tomography; D=day; DLT=dose-limiting toxicity; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; HBsAg=hepatitis B surface antigen; HBcAb=hepatitis B core antibody; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HL=Hodgkin's lymphoma; 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=pharmacokinetics; PR=partial response; PT=prothrombin time; QTcF=corrected QT interval with Fridericia; 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, 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 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 Cycle 1 Day 1, 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 pressure 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, reticulocyte count, white blood cell count with differential (neutrophils, bands, 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.

[16] All women who are not postmenopausal (≥12 months of nontherapy-induced amenorrhea) or surgically sterile 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/or 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, 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-points tables in Appendix 2 and Appendix 3 of protocol Amendment 5. At the sponsor's discretion, some patients in the expansion stage may be required to provide samples for pharmacodynamics analysis. This will be based on certain signals as determined by the study team. The time points for these pharmacodynamic samples will be determined at the time of patient selection.

[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. CTCAE CRITERIA TABLE FOR LAB PARAMETERS

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Hemoglobin (g/L)	Anemia	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	~
			Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L	~
Platelets (10^9/L)	Platelet count decreased		<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Neutrophils (10^9/L)	Neutrophil count decreased		<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Lymphocytes (10^9/L)	Lymphocyte count decreased		<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
		Lymphocyte count increased	~	>4000/mm3 - 20,000/mm3	>20,000/mm3	~
Eosinophils (10^9/L)		Eosinophilia	>ULN and >Baseline	~	Steroids initiated	~
Activated Partial Thromboplastin Time (sec)/Activated Partial Thromboplastin Time (RATIO)		Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	~
Prothrombin Intl. Normalized Ratio		INR increased	>1.2 - 1.5	>1.5 - 2.5	>2.5	~
Albumin (g/L)	Hypoalbuminemia		<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	~

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Glucose (mmol/L)	Hypoglycemia		<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
Creatinine (umol/L)		Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline if baseline was abnormal; >1.5 - 3.0 x ULN if baseline was normal	>3.0 x baseline-6.0xULN if baseline was abnormal; >3.0 - 6.0 x ULN if baseline is normal	>6.0 x ULN
Creatine Kinase (IU/L)		CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN- 5 x ULN	>5.0 X ULN - 10.0 x ULN	>10.0 x ULN
Alkaline Phosphatase (IU/L)		Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; [a] 2.0 - 2.5 x baseline if baseline was abnormal [b]	>2.5 - 5.0 x ULN if baseline was normal; [a] >2.5 - 5.0 x baseline if baseline was abnormal [b]	>5.0 - 20.0 x ULN if baseline was normal; [a] >5.0 - 20.0 x baseline if baseline was abnormal [b]	>20.0 x ULN if baseline was normal; [a] >20.0 x baseline if baseline was abnormal [b]
Aspartate Aminotransferase (IU/L)		Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; [a] 1.5 - 3.0 x baseline if baseline was abnormal [b]	>3.0 - 5.0 x ULN if baseline was normal; [a] >3.0 - 5.0 x baseline if baseline was abnormal [b]	>5.0 - 20.0 x ULN if baseline was normal; [a] >5.0 - 20.0 x baseline if baseline was abnormal [b]	>20.0 x ULN if baseline was normal; [a] >20.0 x baseline if baseline was abnormal [b]
Alanine Aminotransferase (IU/L)		Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; [a] 1.5 - 3.0 x baseline if baseline was abnormal [b]	>3.0 - 5.0 x ULN if baseline was normal; [a] >3.0 - 5.0 x baseline if baseline was abnormal [b]	>5.0 - 20.0 x ULN if baseline was normal; [a] >5.0 - 20.0 x baseline if baseline was abnormal [b]	>20.0 x ULN if baseline was normal; [a] >20.0 x baseline if baseline was abnormal [b]

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Calcium (mmol/L)	Hypocalcemia	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
			<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Magnesium (mmol/L)	Hypomagnesemia	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	~	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
			<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Potassium (mmol/L)	Hypokalemia	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
			<LLN - 3.0 mmol/L	~	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Cholesterol (mmol/L)		Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Bilirubin (umol/L)		Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; [a] > 1.0 - 1.5 x baseline if baseline was abnormal [b]	>1.5 - 3.0 x ULN if baseline was normal; [a] >1.5 - 3.0 x baseline if baseline was abnormal [b]	>3.0 - 10.0 x ULN if baseline was normal; [a] >3.0 - 10.0 x baseline if baseline was abnormal [b]	>10.0 x ULN if baseline was normal; [a] >10.0 x baseline if baseline was abnormal [b]
Triglycerides (mmol/L)		Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Urine Protein		Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0-<3.5g/24hrs	4+ proteinuria; urinary protein >= 3.5g/24hrs	~

			ATOXGR			
PARAM (SI Unit)	**Hypo**	**Hyper**	**GRADE 1**	**GRADE 2**	**GRADE 3**	**GRADE 4**
Lactate Dehydrogenase (IU/L)		Blood lactate dehydrogenase increased	>ULN	~	~	~
Gamma Glutamyl Transferase (IU/L)		GGT increased	>ULN - 2.5 x ULN if baseline was normal; [a] 2.0 - 2.5 x baseline if baseline was abnormal [b]	>2.5 - 5.0 x ULN if baseline was normal; [a] >2.5 - 5.0 x baseline if baseline was abnormal [b]	>5.0 - 20.0 x ULN if baseline was normal; [a] >5.0 - 20.0 x baseline if baseline was abnormal [b]	>20.0 x ULN if baseline was normal; [a] >20.0 x baseline if baseline was abnormal [b]
Urate (umol/L)		Hyperuricemia	>ULN	~	~	~
pH		Alkalosis	pH >normal, but <=7.5	~	pH >7.5	~
	Acidosis		pH <normal, but >=7.3	~	pH <7.3	~
Leukocytes (10^9/L)		Leukocytosis	~	~	>100,000/mm3	~
	White blood cell decreased		<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L

LLN = Lower limit of normal, ULN = Upper limit of normal; ~ = Not applicable

[a] If the baseline value is normal, the toxicity grade will be determined by the post-baseline value and the ULN (e.g., > ULN – 2.5 x ULN).

[b] If the baseline value is abnormal, the toxicity grade will be determined by the baseline value and the post-baseline value (e.g., 2.0 – 2.5 x baseline). This rule only applies to the abnormal baseline value that is higher than the normal range upper limit.

APPENDIX 3. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times
Depending on data available, dates and times will take the form yyyy-mm-dd and hh:mm:ss.

Spelling Format
English US (or English UK).

Presentation of Treatment Groups
All summaries will be presented by assigned dose level. Dose expansion stage patients will be included in their dose level group and presented together with dose escalation patients receiving the same dose level.

Listings
All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment group (ascending dose level in Stage 1, and Stage 2: CLL/SLL, FL, MZL, LPL/WM, MCL, PTCL, and CBCL)
- Patient ID,
- Visit (where applicable)
- Date (where applicable),

For listings where screen failed patients are included, these will appear in a category after the other treatment groups labeled 'Screen Failed'.

APPENDIX 4. INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA (IWCLL) UPDATE OF THE NATIONAL CANCER INSTITUTE-WORKING GROUP (NCI-WG) GUIDELINES: RESPONSE CRITERIA

Complete Response (CR)

CR requires all of the following criteria as assessed no earlier than 2 months after completion of therapy:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4,000/μL)
- Absence of significant lymphadenopathy (nodes ⩽ 15 mm in longest diameter or any extra nodal disease) by physical examination and 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 [100,000/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 last treatment when clinical and laboratory results listed above demonstrate a CR/cytopenic CR has been achieved. Bone marrow at least normocellular for age, < 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 pre-treatment 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 of primarily T cells or lymphocytes other than CLL cells, or CLL cells. Patients with residual CLL cells should be considered to be PR (nPR).

CR with incomplete bone marrow recovery (CRi)

Patients who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia; anemia, thrombocytopenia or neutropenia. The bone 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

- ⩾ 50% reduction in lymphadenopathy (sum of longest diameter of the 6 largest lymph nodes by physical exam and 50% reduction in the sum of product of diameter (SPD) 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 one of the following:

- Neutrophils > 1.5 × 10^9/L [1500/μL] (without growth factors) or ⩾ 50% increase of pre-treatment value
- Platelets > 100 × 10^9/L [100,000/μL] (without platelet transfusion growth factors) or ⩾ 50% increase of pre-treatment 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 partial response 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

Progressive disease (PD) during or after therapy will be characterized by at least one 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 (i.e. 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 [PLL] 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 by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100,000/μL)

Which occurs no earlier than 3 months after end of therapy defines progression if the marrow biopsy demonstrates an infiltrate 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 stable disease

Overall Response Rate (ORR)

Response is classified into classical-ORR, defined as the proportion of patients with CR, complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), or partial response (PR), as determined by the investigator; and neo-ORR defined as the proportion of patients with CR, complete response with incomplete marrow recovery (CRi), nodular partial response (nPR), partial response with lymphocytosis (PR-L) or partial response (PR), as determined by the investigator.

Adapted from:

Hallek M. et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia Blood. 2008 Jun 15;111(12):5446-56.

Cheson B. et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. Journal of Clinical Oncology, 2012 Vol 30,No 23, 2820-2822.

[a] Bone marrow biopsies should be performed at least 3 months after completion of therapy.

APPENDIX 5. CONSENSUS-BASED UNIFORM RESPONSE CRITERIA FOR WM DEVELOPED BY THE IWWM, UPDATED IN THE SIXTH IWWM

Response category	Description
Complete Response (CR)	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 (VGPR)	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 (PR)	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 (MR)	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 (SD)	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 (PD)	⩾25% increase in serum IgM level[a, b] from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

Adapted from: Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood. 2014 Aug 28;124(9):1404-11 Meletios A. Dimopoulos

[a] Sequential changes 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 .5 g/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.

APPENDIX 6. LUGANO RESPONSE CRITERIA FOR HODGKIN AND NON-HODGKIN LYMPHOMA

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

Response and Site	**PET-CT–Based Response**	**CT-Based Response**
	At end of treatment, these findings indicate residual disease	For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from 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 progressive disease 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
Progressive disease	**Progressive metabolic disease**	**Progressive disease 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:

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

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

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in 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 six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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.

STATISTICAL ANALYSIS PLAN

2018-523-00US1

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

AUTHOR: PPD [redacted]

VERSION NUMBER AND DATE: V1.0, 22JUN2023

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 22JUN2023) for Protocol 2018-523-00US1.

	Name	Signature	Date
Author:	PPD		
Position:			
Company:	IQVIA		
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V1.0 (Dated 22JUN2023) for Protocol 2018-523-00US1.

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Upon review of this document, the undersigned approves this version of the Output Templates, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	22JUN2023	PPD	Not Applicable – First Version

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AICC	Akaike's information criterion
AUC_{0-t}	Area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve for the dosing interval
AUC_{tau}/D	Dose-normalized AUC_{tau}
BLQ	Below the limit of quantitation
BTK	Bruton's tyrosine kinase
C_{avg}	Average concentration
CBCL	Cutaneous B-cell lymphoma
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration
C_{max}/D	Dose-normalized C_{max}
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DLT	Dose limiting toxicity
eCRF	Electronic case report form
FAS	Full analysis set
FL	Follicular lymphoma
GCV	Geometric coefficient of variation
GeoMean	Geometric mean
HL	Hodgkin lymphoma
LS	Least-squares
MCL	Mantle cell lymphoma
$MRAUC_{tau}$	Metabolite to parent ratio for AUC_{tau}
MRC_{max}	Metabolite to parent ratio for C_{max}
M/T $RAUC_{tau}$	Metabolite to total drug ratio for AUC_{tau}
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
MW	Molecular weight
n	Number of observations
N	Number of subjects
PK	Pharmacokinetics
PKAS	Pharmacokinetics analysis set

Abbreviation	Definition
PTCL	Peripheral T-cell lymphoma
PTR	Peak to trough ratio
QD	Once a day (from the Latin quaque die)
$R_{A(AUC)}$	Accumulation ratio for AUC_{tau}
$R_{A(Cmax)}$	Accumulation ratio for C_{max}
RP2D	Recommended Phase 2 dose
SAP	Statistical analysis plan
SD	Standard deviation
$t_{1/2,eff}$	Effective half-life
TEAEs	Treatment-emergent adverse events
TimeHigh	Time above the IC_{90} level
t_{max}	Time to reach maximum plasma concentration
t_{min}	Time to reach minimum plasma concentration
WM/LPL	Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of pharmacokinetic (PK) data for Protocol 2018-523-00US1. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol Amendment 4, dated 12 December 2022 and pertains to the analysis of secondary and exploratory PK objectives only.

3. STUDY OBJECTIVES

3.1. SECONDARY OBJECTIVE

The secondary PK objective is 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.

3.2. EXPLORATORY OBJECTIVE

The exploratory PK objective is to evaluate the PK properties of the major metabolites of HMPL-523 in patients with relapsed or refractory lymphoma in the dose escalation and dose expansion stages.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

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.

Dose Escalation Stage (Stage 1)

Dosing will begin at 100 mg 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 maximum tolerated dose (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 dose limiting toxicity (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. The study will enroll approximately 6 to 30 patients in the dose escalation stage. See Table 1 below for the proposed dose escalation scheme.

Table 1: Proposed Dose Escalation Scheme

Cohort	Dose
1	100 mg QD Orally, with water, after meal
2	200 mg QD Orally, with water, after meal
3	400mg QD Orally, with water, after meal
4	600mg QD Orally, with water, after meal
5	800mg 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. Based on evaluation of data collected during the dose escalation phase, the recommended Phase 2 dose (RP2D) has been determined to be 700 mg once daily.

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.

Dose Expansion Stage (Stage 2)

The safety, tolerability, PK, and preliminary efficacy of HMPL-523 at the MTD/R2PD will be further evaluated in patients with relapsed or refractory non-Hodgkin's and Hodgkin's lymphomas.

In the dose expansion stage, as of Protocol Amendment 3, approximately 125 patients may enroll in the cohorts listed below:

- Chronic lymphocytic leukemia (CLL) (n=10)
- CLL post-Bruton's tyrosine kinase (BTK) exposure (n=20)
- Mantle cell lymphoma (MCL) (n=10)
- Follicular lymphoma (FL) (Grade 1-3a) (n=20)
- Marginal zone lymphoma (MZL) (n=10)
- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) (n=10)
- Peripheral T-cell lymphoma (PTCL) (n=10)
- Cutaneous B-cell lymphoma (CBCL) (n=10)
- Hodgkin lymphoma (HL) (n=10)

As of 30 November 2022, per implementation of Protocol Amendment 4, patients will no longer be permitted to consent to enroll in selected lymphoma dose expansion cohorts (MCL, FL, MZL, WM/LPL, PTCL, and CBCL). The following cohorts will continue enrollment with approximately 55 patients across cohorts as listed below:

- CLL (n=10)
- CLL post-BTK exposure (n=20, of which approximately 10 should also have prior BCL-2 inhibitor therapy)
- HL (n=25)

Patients will receive HMPL-523 at the MTD/RP2D, (700 mg) orally, once daily, continuously for 28 days in a treatment cycle, and repeatedly 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.

4.2. DETERMINATION OF SAMPLE SIZE

Upon implementation of Protocol Amendment 4, approximately 90 patients are expected to be enrolled in the study, including 20 patients in the dose escalation stage and approximately 70 patients in the dose expansion stage.

4.3. SCHEDULE OF EVENTS

Schedule of events can be found in APPENDIX 1 of the protocol. The PK sampling time points for the dose escalation stage and dose expansion stage can be found APPENDIX 2 in and APPENDIX 3 of the protocol, respectively.

4.4. CHANGES TO ANALYSIS FROM PROTOCOL

Not applicable.

5. PLANNED ANALYSES

All final, planned analyses identified in this SAP will be performed by IQVIA Early Clinical Development (ECD) Biostatistics group following Sponsor authorization of this SAP, Database Lock, and receipt of data by IQVIA.

6. ANALYSIS SETS

6.1. FULL ANALYSIS SET (FAS)

The Full Analysis Set (FAS) is defined as all patients who received at least one dose of HMPL-523. This population will be used for the PK sample collection listing.

6.2. PHARMACOKINETICS ANALYSIS SET (PKAS)

The Pharmacokinetics Analysis Set (PKAS) is defined as all patients who received at least one dose of HMPL-523 and have at least one quantifiable plasma concentration without protocol violations or events with potential to affect the PK concentrations. Subjects in this population will be used for all PK analyses.

7. GENERAL CONSIDERATIONS

Derivation of plasma PK parameters for HMPL-523 treatment will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK summaries, summary figures, and data listings as well as the statistical analysis of the PK variables will be the responsibility of the PK study biostatistician/PK programmer at IQVIA. Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

7.1. SUMMARY STATISTICS

Plasma concentrations of HMPL-523 and its metabolites will be summarized separately for Stage 1 and Stage 2 as appropriate (for $n \geq 3$ only) by cohort/dose level, cycle, day, and nominal time point using N (number of subjects), n (number of observations), arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, and maximum using the PK analysis set. If $n<3$, then only n, minimum, and maximum will be presented. Stage 2 serial sampling concentration data collected after a dose change will only be included in listings.

Pharmacokinetic parameters for HMPL-523 and its metabolites will be summarized separately for Stage 1 and Stage 2 as appropriate (for $n \geq 3$ only) by cohort/dose level, cycle, and day using N, n, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean (GeoMean), and geometric CV (GCV) using the PK analysis set. If $n<3$, then only n, minimum, and maximum will be presented. Arithmetic mean, SD, CV, GeoMean, and GCV will not be calculated for t_{max} and t_{min}. A subject listing of individual PK parameters for each treatment will be provided. Stage 2 PK parameters calculated from serial sampling concentration data collected after a dose change will only be included in listings.

7.2. TREATMENT SUMMARIZATION

In general, Stage 1 data will be presented by cohort/dose level as Cohort X (YY mg QD) [for example, Cohort 1 (100 mg QD)]. Stage 2 data will be summarized by cohort/disease group [for example, Cohort 1 (CLL)].

7.3. PRECISION

All PK concentrations will be reported and analyzed with the same precision as the source data provided by bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Unrounded PK (exported from Phoenix WinNonlin) will be considered the source data for the calculation of descriptive statistics and the statistical analysis. Derived PK parameters will be rounded for reporting purposes in by-subject listings. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, C_{max} and C_{min}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, t_{max} and t_{min}) will be reported with the same precision as the actual elapsed sampling time value of the source data which shall be pre-specified as 2 decimal places with unit of hours.
- If a value is greater than 1000, it will be rounded to the nearest whole number.

For the reporting of descriptive statistics, the mean (arithmetic and geometric), and SD will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation and GCV will always be reported to 1 decimal place.

For inferential statistics, geometric least-squares (LS) mean ratios will be presented as a percentage (with 2 decimal places). P-values, if any, shall be reported to 4 decimal places or as <0.0001.

7.4. SOFTWARE VERSION

All derivations, statistical analyses, and associated statistical outputs (tables, figures, and

listings) will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, Princeton, New Jersey). Graphics will be prepared using the same version of SAS.

8. STATISTICAL CONSIDERATIONS

8.1. MISSING DATA

Missing PK concentrations will be handled as described in Section 10.1.

9. PROTOCOL DEVIATIONS

9.1. DEVIATIONS AND SIGNIFICANT EVENTS RELATED TO PK ANALYSIS

Changes to the procedures or events which may impact the quality of the PK data will be considered significant protocol deviations or events and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, dose or dosing regimen changes or missed doses that affect PK, concomitant medication usage likely to affect PK, vomiting following oral dosing occurring within the time frame of 2 times the median t_{max}, large time deviations at important time points, and sample processing errors that lead to inaccurate bioanalytical results. In the case of a significant protocol deviation or event, affected PK data may be excluded from analyses and summaries.

10. PHARMACOKINETICS

10.1. VARIABLES AND DERIVATIONS

10.1.1. PLASMA CONCENTRATION DATA

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A subject listing of all concentration-time data (HMPL-523 and its metabolites, including but not limited to M1 and M44) following HMPL-523 QD dosing will be presented by cohort/dose level/cycle, subject, and scheduled sample collection time.

Serial sampling concentration data will be summarized for the PKAS by stage, cohort/dose level, cycle, Day (1, 15, 28) and nominal time point using N, n, arithmetic mean, SD, CV, minimum, median, and maximum. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. If n<3, then data will not be summarized, with the exception of n, minimum, and maximum. Unscheduled measurements will not be included in summary statistics. PK samples obtained in the Dose Expansion Stage within 14 to 28 days after a dose change will not be included in summary statistics. Listings will include all scheduled and unscheduled PK concentration data. In case a PK sample was collected outside the sampling windows defined in the protocol, the PK concentration results may be excluded from the summaries.

Graphs will be presented to illustrate the data for HMPL-523 (and metabolites if applicable) in Stage 1 and Stage 2 parts of the study as follows:

Stage 1 (Dose Escalation):

- Mean (±SD) concentration-time data by Day (Days 1, 15, and 28; one plot for each day with all dose levels in the same plot) for HMPL-523 (and metabolites if applicable) following QD administration will be presented on linear and semilogarithmic scale.
- Mean (±SD) concentration-time data for HMPL-523 (and metabolites if applicable) by dose level (one plot for each dose level with all days in the same plot) following QD administration will be presented on linear and semilogarithmic scale.
- By-subject plots with concentration profiles for HMPL-523 (and metabolites if applicable)

on Days 1, 15, and 28 will be presented on linear and semilogarithmic scale in the same graph.

- Mean (±SD) trough concentrations on Cycle 1 Day 2, Day 15 (±1), Day 16 (±1), and Day 28 (±3) and Cycle 2 Day 1 (±3) (ie, Day 29 relative to Cycle 1) will be presented for HMPL-523 (and metabolites if applicable) on a linear scale as scatter plots versus time in days from start of treatment (numeric scale) for each cohort/dose level. Attainment of steady state for HMPL-523 will be evaluated graphically by evaluating these trough concentrations over this period.

Stage 2 (Dose Expansion Stage):

- Mean (±SD) concentration-time data for HMPL-523 (and metabolites if applicable) at RP2D by Day (all disease groups with n≥3 in one plot) following QD administration will be presented on linear and semilogarithmic scale.
- By-subject plots with concentration profiles for HMPL-523 (and metabolites if applicable) by Day will be presented on linear and semilogarithmic scale in the same graph.
- Mean (± SD) trough concentrations on Cycle 1 Day 2 and Day 28 (±3), Cycle 2 Day 1 (±3), Cycle 3 Day 1 (±3), Cycle 5 Day 1 (±3) and every other cycle thereafter will be presented for HMPL-523 (and metabolites if applicable) at RP2D on a linear scale as scatter plots versus time in days from start of treatment (numeric scale) for each disease group.

10.1.2. PHARMACOKINETIC PARAMETERS

Subjects with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters. Pharmacokinetic parameters following database lock will be calculated for HMPL-523 (and its metabolites, including but not limited to M1 and M44) by noncompartmental methods, using actual elapsed time from dosing.

For PK parameter calculations following single dose (Day 1 of Cycle 1), predose samples that are BLQ or missing will be assigned a numerical value of zero. Any anomalous concentration values observed at predose on Day 1 of Cycle 1 will be identified in the study report and used for the computation of PK parameters. If the anomalous concentration is greater than 5% of C_{max}, the PK parameters for the given subject will be calculated and reported in the listing and considered on a case-by-case basis for exclusion from statistical summaries and analyses. Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial

portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between two quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile, and the consecutive BLQ concentrations will also be set to missing.

The following single dose plasma PK parameters will be calculated (if estimable) on Day 1 of Cycle 1 (C1D1) for HMPL-523 (and metabolites if applicable) following QD dosing for Stage 1 and Stage 2:

C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data.
t_{max}	Time to maximum concentration, obtained directly from the observed concentration versus time data.
AUC_{0-t}	Area under the concentration-time curve from time zero (predose) to time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
AUC_{tau}	Area under the concentration-time curve during a dosing interval, tau (tau = 24 h), calculated by linear up/log down trapezoidal summation. Note: The following conventions will be followed for the calculation of the parameter: • AUC_{all} will be used as an estimate of AUC_{tau} if concentrations fall to BLQ at or before reaching tau unless otherwise warranted by the data. For this, the BLQ will be set to zero. • This parameter will not be calculated if the data is missing at tau. • If the time deviation at time tau is significant, the analyst may consider listing the AUC_{tau} estimate but excluding the estimate (and related parameters) from summaries and analyses.
C_{max}/D	Dose-Normalized C_{max}, calculated as C_{max} divided by dose.

AUC_{tau}/D	Dose-Normalized AUC_{tau}, calculated as AUC_{tau} divided by dose.

The following plasma PK parameters will be estimated for HMPL-523 (and metabolites if applicable) following multiple dosing on Days 15 and 28 of Cycle 1 for Stage 1 and Day 28 of Cycle 1 (and 14-28 days after a dose change in subsequent cycles) for Stage 2 where data is collected and available:

C_{max}	Maximum concentration after multiple dosing, obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum concentration, obtained directly from the observed concentration versus time data.
C_{min}	Minimum observed concentration after multiple dosing, obtained directly from the observed concentration versus time data.
t_{min}	Time of minimum concentration, obtained directly from the observed concentration versus time data.
AUC_{tau}	Area under the plasma concentration-time curve during a dosing interval (tau =24 h), calculated by linear up/log down trapezoidal summation. Actual elapsed time will be used for the calculation, unless otherwise specified below. The following conventions will be followed for missing or BLQ data at tau on study Days 15 and 28 (Cycle 1): • If the concentration at predose is missing, then the concentration will be set to equal the concentration measured at tau [assuming linear PK and steady-state conditions, and that the tau sample was collected within a window of ±1 hour of the scheduled time postdose for the calculation of AUC_{tau} but prior to the next dose]. • If no sample is collected at the end of the dosing interval or data are missing at the end of the dosing interval, the concentration will be set equal to the predose value (assuming linear PK and steady-state conditions, and that the predose collection was valid) and tau will be set to the nominal time for the calculation of AUC_{tau}, if appropriate. • AUC_{all} (if appropriate) shall be used as an estimate of AUC_{tau} if

	concentrations fall to BLQ at or before reaching tau unless otherwise warranted by the data. For this the BLQ will be set to zero. • If the time deviation at time tau is significant (outside of the window of ±1 hour of the scheduled time postdose), the parameter will not be calculated.
C_{avg}	Average concentration over the dosing interval tau, calculated as AUC_{tau} divided by the dosing interval, tau [tau: 24, actual time will be used. See above for window for 'tau'].
PTR	Peak to trough ratio, calculated as C_{max}/C_{min}
$R_{A(AUC)}$	Accumulation ratio, calculated for AUC_{tau} on Days 15 and 28 as [AUC_{tau} on C1Dx /AUC_{tau} on C1D1], where x is Day 15 or Day 28.
$R_{A(Cmax)}$	Accumulation ratio, calculated for C_{max} on Days 15 and 28, as [C_{max} on C1Dx/C_{max} on C1D1], where x is Day 15 or Day 28.
$t_{1/2,eff}$	Effective half-life, calculated as $-0.693*tau / \ln(1-1/R_{A(AUC)})$
TimeHigh	Time above the IC_{90} level of 123 ng/mL
CL/F	Apparent systemic clearance, calculated as dose divided by AUC_{tau}. (Only for HMPL-523).
C_{max}/D	Dose-Normalized C_{max}.
AUC_{tau}/D	Dose-Normalized AUC_{tau}.
MRC_{max}	Ratio of metabolite C_{max} to parent HMPL-523 C_{max}, calculated for each metabolite as (metabolite C_{max}/metabolite MW) / (parent C_{max}/parent MW).
$MRAUC_{tau}$	Ratio of metabolite AUC_{tau} to parent HMPL-523 AUC_{tau}, calculated for each metabolite as (metabolite AUC_{tau}/metabolite MW) / (parent AUC_{tau}/parent MW).
M/T $RAUC_{tau}$	Ratio of metabolite AUC_{tau} to total drug AUC_{tau}, calculated for each metabolite as (metabolite AUC_{tau}/metabolite MW) / (parent AUC_{tau}/parent MW + metabolite M1 AUC_{tau}/metabolite M1 MW + metabolite M44 AUC_{tau}/metabolite M44 MW).

C=cycle; D=Day; MW=molecular weight

Concentrations as supplied by the bioanalytical laboratory will be used in the PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will

be presented as they are received from the bioanalytical laboratory.

C_{max}, C_{min}, t_{max}, and t_{min} will be obtained directly from the concentration-time profiles. In case of multiple peaks, the highest postdose concentration will be reported as C_{max}. In case of multiple peaks of equal magnitude, the earliest t_{max} will be reported.

For calculation of the metabolite ratio, C_{max} and AUC_{tau} will be adjusted by molecular weight (MW) of the parent drug and metabolite. The MWs are presented below:

- HMPL-523 [$C_{24}H_{30}N_6O_3S$]: 482.60 g/mol (free base)
- M1 or HM5023222 [$C_{24}H_{30}N_6O_4S$]: 498.60 g/mol
- M44 or HM5025866 [$C_{31}H_{38}N_6O_{11}S$]: 702.73 g/mol

Based on the formulation for HMPL-523, no dose adjustment calculations need to be made for any molecular conversions between administered drug product and analyte measured.

Scatter plots of individual and geometric mean PK parameters [C_{max}, AUC_{tau}, C_{max}/D, and AUC_{tau}/D] will be presented for Cycle 1 Days 1, 15, and 28 to assess the relationship between dose and PK exposure for HMPL-523 and its metabolites.

Pharmacokinetic parameters for HMPL-523 and its metabolites will be summarized for the PKAS by stage, cohort/dose level, cycle, and day using N, n, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean (GeoMean), and geometric CV (GCV) using the PK analysis set. If n<3, then only n, minimum, and maximum will be presented. Arithmetic mean, SD, CV, GeoMean, and GCV will not be calculated for t_{max} and t_{min}. A subject listing of individual PK parameters for each treatment will be provided. Stage 2 PK parameters calculated from serial sampling concentration data collected after a dose change will only be included in listings.

10.1.3. Statistical Analysis of PK Parameters

For the dose escalation stage (Stage 1), dose proportionality of PK parameters, C_{max} and AUC_{tau} over the administered dose range will be assessed graphically for Days 1, 15, and 28 of Cycle 1. Dose proportionality of HMPL-523 and its metabolites will also be statistically evaluated as an

exploratory analysis using the power model approach, using the following model:

$$\ln(Y_i) = \beta_0 + \beta_1 \ln(D_i) + \varepsilon_i$$

where Y_i is the PK parameter for subject i, D_i is the dose, ε_i is the random error and β_0 and β_1 are the intercept and the slope of the model, respectively. The intercept β_0 and the slope β_1 will be estimated with 90% confidence interval (CI) for each PK parameter. Parameters will be estimated using ordinary LS approach or equivalent. Dose proportionality will be declared if 90% CI for slope parameter lies entirely within the critical interval [$1+\log_e(0.8)/\log_e(r)$, $1+\log_e(1.25)/\log_e(r)$], where r=highest dose level/lowest dose level, ie, the ratio of the highest dose level to the lowest dose level administered in the study [1]. For an example, if the highest dose level administered in the study is 800 mg QD as planned in the protocol, then r=800/100=8 (ie, 8-fold increase in dose) and dose proportionality will be declared if 90% CI for slope parameter lies entirely within the critical interval [0.89, 1.11]. The actual critical region to be used for declaring dose proportionality will depend on the highest dose administered in this study.

For the dose escalation stage (Stage 1), time to steady state HMPL-523 will be evaluated graphically. In addition to the graphical assessment of the steady state for HMPL-523 and where data are available, a statistical evaluation of the steady state will also be made using the trough (predose) plasma concentrations collected on Days 2 (C1D2), 15 (C1D15), 16 (C1D16), 28 (C1D28), and 29 (C2D1). For each dose level separately, all valid concentrations on the natural-log scale will be analyzed using a repeated-measures linear mixed effect model with PK day (i.e., protocol nominal day) as a fixed-repeated effect. From this model, orthogonal contrasts with 90% CI will be formed between the adjusted mean concentration at each protocol nominal day (earlier day) and the mean concentrations for all the following protocol nominal days (latter days) using Helmert contrasts. Precisely, Day 2 will be compared to Days 15 through 29 and so on. Prior to estimating the fixed effects and the contrasts, an appropriate treatment-specific covariance structure will be selected using corrected Akaike's information criterion (AICC). These contrasts will be statistically compared to zero at the 5% significance level, with the one-sided alternative that the latter day mean is higher than the early day mean. Assessment of the time to reach steady state from the statistical analysis will be based on the earliest day at which a contrast is determined to be not statistically significant at 5% level of significance. For reporting of steady-state comparisons, the contrasts will be back-transformed to the original scale, to yield the ratio of latter day mean concentration to earlier day mean concentration.

Similarly, the 90% CI for the ratio of means will be calculated and reported with the p-value of the contrast. If the estimate of time to reach steady state based on the statistical analysis described above seems inconsistent with visual inspection of the graphical displays of mean PK trough concentrations over time, clinical judgment may supersede the statistical assessment.

11. REFERENCES

1. Smith BP, et al. Confidence Interval Assessment of Dose Proportionality. *Pharm Res*. 2000;17:10.