Statistical Analysis Plan	
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A Phase 1/2 Open Label, Multi-center Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Acalabrutinib in Chinese Adult Subjects with Relapsed or Refractory Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia or other B-cell Malignancies

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
5PS	5-point scale
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUCinf	Area under the plasma concentration-time curve (from zero to infinity)
AUC0-12	Area under the plasma concentration-time curve (from zero to 12 hours)
AUClast	Area under the plasma concentration-time curve (from zero to the time of the last quantifiable concentration)
AUCτ	Area under the plasma concentration-time curve across the dosing interval; e.g. For BID dosing, AUC0-12 is the AUC_{τ} after single dose
BICR	Blinded Independent Central Review
BID	Twice daily
BOR	Best overall response
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CLL	Chronic lymphocytic leukemia
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Cmax	Maximum observed plasma drug concentration
CR	Complete response
CRi	CR with incomplete marrow recovery
CSP	Clinical Study Protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology group
eCRF	Electronic Case Report Form
EoT	End of Treatment

Abbreviation or special term	Explanation
FDG	[^{18}F] fluorodeoxyglucose
FL	Follicular lymphoma
GI	Gastrointestinal
anti-HBc	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IHC	Immunohistochemistry
IP	Investigational product
IPD	Important protocol deviation
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
LDH	Lactate dehydrogenase
LDi	Longest transverse diameter of a lesion
λz	Terminal elimination rate constant
λzN	Number of data points used for λz determination
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	MCL international prognostic index
MRI	Magnetic resonance imaging
MRD	Minimal residual disease
Metabolite: Parent ratio (AUC)	Metabolite-to-parent ratio; AUC(metabolite)/AUC(parent)
Metabolite: Parent ratio (Cmax)	Metabolite-to-parent ratio; Cmax,(metabolite)/Cmax(parent)
NA	Not applicable
NE	Non-evaluable
NHL	Non-Hodgkin lymphoma
nPR	Nodular partial response
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction

Abbreviation or special term	Explanation
PD	Progression of disease
PE	Physical exam
PET	Positron-emission tomography
PFS	Progression free survival
PK	Pharmacokinetics
PPD	Cross product of the LDi and perpendicular diameter
PR	Partial response
PR	Partial remission (response)
PRL	Partial response with lymphocytosis
QD	Once per day (dosing)
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
Rac AUC	Accumulation ratio calculated as AUCτ(steady state)/AUCτ(first dose)
Rac Cmax	Accumulation ratio calculated as Cmax(steady state)/Cmax(first dose)
RR	The time between corresponding points on 2 consecutive R waves on ECG
R/R	Relapsed/refractory
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SDi	Shortest axis perpendicular to the LDi
SoA	Schedule of Activities
SLL	Small Lymphocytic Lymphoma
SRC	Safety Review Committee
SPD	Sum of the product of the perpendicular diameters for multiple lesions
t½λz	Half-life associated with terminal slope (λz) of a semilogarithmic concentration-time curve
T/B/NK cells	T-lymphocyte/B-lymphocyte/natural killer cells
TCP	Temporal change parameter in systemic exposure (also known as: time dependency, temporal parameter change, linearity index); calculated as AUC_{τ}(steady state)/AUCinf(first dose)

Abbreviation or special term	Explanation
TEAE(s)	Treatment-emergent adverse events
tmax	Time to reach maximum observed concentration
TTR	Time to response
TTNT	Time to next treatment
ULN	Upper limit of normal
Vz/F	Volume of distribution (apparent) following extravascular administration (based on terminal phase)

AMENDMENT HISTORY

Date	Brief description of change
14June2022	• Updates based on CSP amendment (v6.0) • IPD list update per Non-compliance Handling Plan V6.0. • Update from AstraZeneca Drug dictionary to WHODRUG dictionary • Added output for hematological parameters of clinical interest • Updated ECI definitions and narrative search criteria per updated MedDRA version.
23Aug2021	• Updates based on CSP amendment (v5.0) • Added clarifications and reformulations in sections 3 and 4. • Added outputs in sections 4 to be consistent with TLF shells and sponsor requirements.

1. STUDY DETAILS

1.1. Study objectives

Table 1 Study objectives

Phase 1 Portion - Primary Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of acalabrutinib in Chinese subjects with Relapsed/Refractory (R/R) B-cell malignancies	Adverse events (AEs), laboratory data, vital signs, and Electrocardiograms (ECGs)
To characterize pharmacokinetics of acalabrutinib and its major metabolite (ACP-5862) in Chinese subjects with R/R B-cell malignancies	AUCinf, AUC0-12, AUClast, Cmax, tmax, CL/F (acalabrutininb only), Vz/F (acalabrutininb only), λz, t½λz, Metabolite: Parent ratio (Cmax), and Metabolite: Parent ratio (AUC) after single dose; AUCτ, Cmax, Cmin, tmax, CL/F (acalabrutinib only), Metabolite: Parent ratio (Cmax), Metabolite: Parent ratio (AUCτ), TCP, Rac AUC and Rac Cmax after multiple doses
Phase 1 Portion - Secondary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies	For R/R chronic lymphocytic leukemia (CLL): Tumor response (number of subjects with CR, CRi, PR, nPR, PRL, SD, PD) For other R/R B-cell malignancies: Tumor response (number of subjects with CR, PR, SD, PD)
Phase 2 Portion Cohort A - Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R mantle cell lymphoma (MCL)	ORR as assessed by Blinded Independent Central Review (BICR) per Lugano classification for Non-Hodgkin Lymphoma (NHL)
Phase 2 Portion Cohort A- Secondary Objective:	**Endpoint/Variable:**
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R MCL	DoR, PFS and TTR as assessed by BICR per Lugano classification for NHL; ORR, DoR, PFS and TTR as assessed by investigators per Lugano classification for NHL; OS
To assess the safety profile of acalabrutinib in Chinese subjects with R/R MCL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R MCL	Plasma concentration of acalabrutinib (sparse sampling)

Table 1 Study objectives

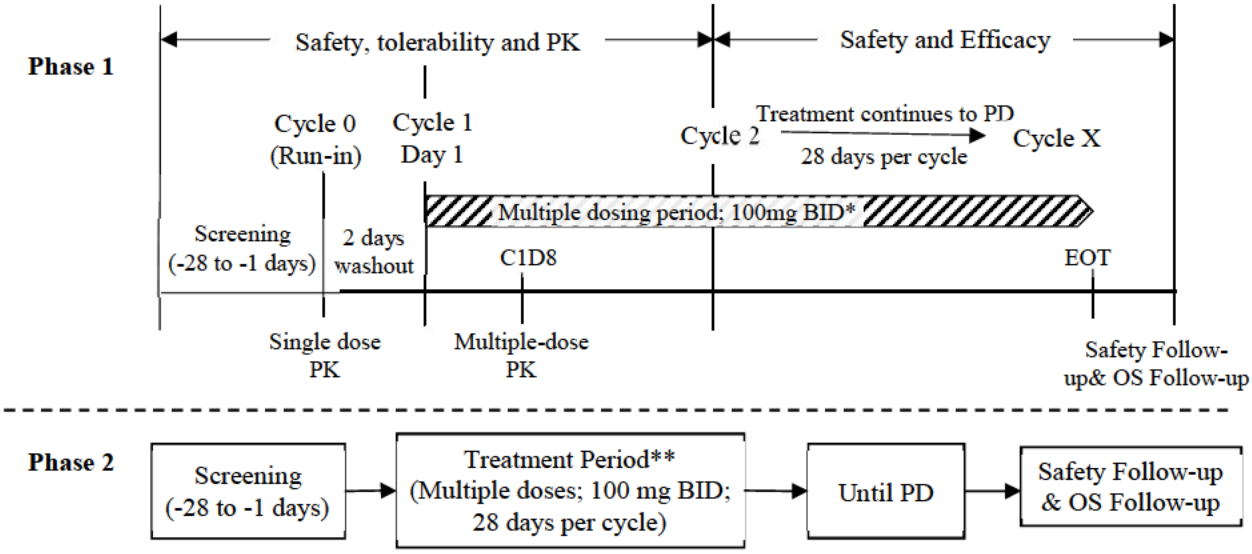
Phase 2 Portion Cohort B - Primary Objective:	**Endpoint/Variable:**
To assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	ORR as assessed by BICR per iwCLL 2018 criteria
Phase 2 Portion Cohort B- Secondary Objective:	**Endpoint/Variable:**
To further assess the efficacy of acalabrutinib in Chinese subjects with R/R CLL	DoR, PFS and TTR as assessed by BICR per iwCLL 2018 criteria; ORR, DoR, PFS and TTR as assessed by investigators per iwCLL 2018 criteria; TTNT; Minimal residual disease negative rate (defined as the proportion of subjects with MRD-negativity) measured in the peripheral blood by flow cytometry; OS
To assess the safety profile of acalabrutinib in Chinese subjects with R/R CLL	AEs, laboratory parameters, vital signs, and ECGs
To assess pharmacokinetics of acalabrutinib in Chinese subjects with R/R CLL	Plasma concentration of acalabrutinib (sparse sampling)
Safety Objectives are contained within the primary and secondary objectives.	

Data from R/R MCL subjects in both Phase 1 and Phase 2 will be combined for analysis.

1.2. Study design

This is an open-label, two-part study to assess the safety, tolerability, pharmacokinetics and clinical efficacy of acalabrutinib in Chinese adult subjects with R/R MCL, R/R CLL and other B-cell malignancies. The study is divided into 2 parts: Phase 1 portion and Phase 2 portion. The general study design is summarized in Figure 1.

Figure 1 Study design



* Dose reduction to 100 mg QD may be considered
** Sparse PK sampling will be collected

Phase 1 portion

The primary objective of Phase 1 portion is to assess the safety, tolerability and pharmacokinetics of acalabrutinib in Chinese subjects with R/R B-cell malignancies and the secondary objective is to access the efficacy of acalabrutinib in Chinese subjects with R/R B-cell malignancies. Approximately 12 subjects will be enrolled in the Phase 1 portion including subjects with R/R non-GCB diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), MCL, CLL, Small Lymphocytic Lymphoma (SLL).

Subjects will be administered a single dose of acalabrutinib 100 mg at Cycle 0 Day 1. During the following 2 days wash-out period, intensive PK samples will be collected before and after the first dose until pre-dose at Cycle 1 Day 1. From Cycle 1 Day 1, subjects will be administered multiple doses of acalabrutinib 100 mg BID on a continuous schedule (28 days per cycle). Intensive PK samples will be collected on Cycle 1 Day 8 for 12-hour PK profile at steady state. Additional sparse PK samples will be collected on Cycle 1 Day 28 to assess time-dependent changes. Treatment with acalabrutinib may be continued for Cycle 2 onwards until disease progression or any other treatment discontinuation criterion is met. All subjects who discontinue the study drug will have a safety follow-up visit 30 (+7) days after the last dose of study drug.

The dose regimen of multiple doses of 100 mg BID has been found to be safe/tolerable and potentially effective in overseas clinical studies in Western and Asian subjects. In case of intolerable toxicity, dose reduction to 100 mg QD may be considered (details in CSP Section 6.6.2). Subjects will continue on treatment with acalabrutinib until a treatment discontinuation criterion is met. All R/R MCL subjects who discontinue study therapy due to reasons other than disease progression will continue on study for post-treatment disease follow up and all

R/R MCL subjects who have disease progression will be followed for survival (see CSP Section 7.1.2) unless they withdraw consent or are lost to follow-up.

Phase 2 portion

Phase 2 portion is to further evaluate clinical efficacy, safety and tolerability in subjects with R/R MCL and R/R CLL. The enrolment of Phase 2 portion will be initiated per Safety Review Committee (SRC) recommendation based on preliminary safety data from Phase 1 portion. Detailed information will be provided in SRC charter. Evaluation of efficacy and safety will be performed independently for each cohort.

Cohort A

Cohort A is to evaluate clinical efficacy, safety and tolerability in subjects with pathologically documented MCL who have relapsed after or were refractory to ≥1 (but not >5) prior treatment regimens. Approximately 33 R/R MCL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Cohort B

Cohort B is to evaluate clinical efficacy, safety and tolerability in subjects with CLL who have failed from ≥ 1 prior systemic therapies. Approximately 60 R/R CLL subjects will be enrolled to receive 100 mg of acalabrutinib BID in repeated 28-day cycles.

Treatment with acalabrutinib may be continued until disease progression or any other treatment discontinuation criterion is met. Dose modification provisions are outlined in CSP Section 6.6.2. Note: Temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to CSP Section 7.1 for more information on assessing disease progression under these circumstances. An early termination visit is required for any subjects who permanently discontinue study drug for any reason (except for death, lost to follow up or withdrawal of consent), including disease progression. In addition to the early termination visit, all subjects who discontinue study drug will have a safety follow-up visit 30 (+ 7) days after his or her last dose of study drug.

All subjects will have hematology, clinical chemistry, and urinalysis safety panels done at screening. Once dosing commences (Cycle 1 Day 1), all subjects will be evaluated for safety, including hematology and clinical chemistry at regular basis.

Tumor assessments for R/R MCL subjects will be performed at 8- to 12-week intervals throughout the study. Tumor assessments for R/R CLL subjects will be performed at 12- to 24-week intervals throughout the study. Refer to CSP Section 1.1 for a comprehensive list of study assessments and their timing. The end of trial is defined as the 3rd analyses for R/R CLL subjects of Phase 2 cohort B, which will occur approximately 24 months after the last R/R CLL subject enrolled into Phase 2.

The primary efficacy analyses (R/R MCL and R/R CLL subjects) will be based on BICR assessment

1.3. Number of subjects

The primary objectives of Phase 1 portion are to evaluate the safety, tolerability and pharmacokinetics (PK) of acalabrutinib. Hence approximately 12 patients will be enrolled in Phase 1 to obtain adequate pharmacokinetic and safety data. Additional patients may be enrolled to ensure at least 8 eligible patients with evaluable single- and multiple-dose PK profiles based on China regulatory considerations.

For Phase 2 of the study, approximately 33 R/R MCL subjects (Cohort A) and 60 R/R CLL subjects (Cohort B) will be enrolled in order to evaluate the efficacy in R/R MCL and R/R CLL subjects. For Cohort A, a sample size of 33 subjects will provide a 95% two-sided confidence interval centered around an expected ORR of 80% that excludes an ORR of 60% as a lower bound. With 60 subjects from Cohort B, an exact binomial test with a nominal one-sided 2.5% significance level will have 90% power to detect the difference between a null hypothesis ORR of 70% and an alternative ORR of 88%.

2. ANALYSIS SETS

2.1. Definition of analysis sets

For purposes of analysis, the following populations are defined:

Analysis set	Description
Safety analysis set	All subjects who received at least one dose of acalabrutinib.
Pharmacokinetics analysis set	All subjects who received at least one dose of acalabrutinib, for whom with reportable acalabrutinib plasma concentration and PK parameter data with no important protocol deviations that may impact PK.
Tumor response analysis set	All subjects who received at least one dose of acalabrutinib and for whom baseline tumor assessment is available.

2.2. Protocol deviations

For this study, the following general categories will be considered important protocol deviations (IPDs) and most of them (programmable IPDs) will be programmatically derived from the electronic case report form (eCRF) data. Few observable IPDs may only be identified by site monitoring activities as the data is not captured in any clinical data base.

- Inclusion criteria deviations
- Exclusion Criteria Deviations
- Discontinuation Criteria for study product met but participant not withdrawn from study treatment

- Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study
- Investigational Product (IP) deviation
- Excluded medications taken
- Deviations to study procedure
- Other Important Deviations

IPD categories are defined and managed by the study team during the IPD reviews throughout the study before database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs output and the Listing of Subjects with IPDs. No deviations will lead to patients being excluded from the analysis sets described in Section 2.1 (with the exception of the pharmacokinetics analysis set, if the deviation is considered to impact upon PK).

A per-protocol efficacy analysis excluding patients with significant protocol deviations is not planned. However, a 'deviation bias' sensitivity analysis may be performed on the ORR endpoint excluding patients with deviations that may affect the efficacy of the trial therapy if >10% of patients in either cohort of Phase 2 portion: Did not have the intended disease or indication.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

3. PRIMARY AND SECONDARY VARIABLES

3.1. Response assessment of NHL(MCL, DLBCL, FL, SLL) and CLL

The efficacy analyses (R/R MCL and R/R CLL subjects) will be based on Blinded Independent Central Review (BICR) assessment and investigator assessment according to relevant response assessment criteria mentioned as below.

Results of this independent review will not be communicated to investigators and the management of patients will be based solely upon the results of the response assessment conducted by the investigator. Please refer section 3.1.3 for more information about BICR assessment. The investigator-assessed visit responses will be used directly for efficacy analyses. The programmatically derived visit responses using investigator assessment may be used for reconciliation purpose only if applicable.

3.1.1. Response assessment criteria for NHL

The Lugano criteria for NHL (Cheson 2014) (see CSP Table 7) will be used to determine each patient's response at each visit. It will also be used to determine if and when a patient has progressed

A baseline pretreatment CT scan with contrast (unless contraindicated) is required for the neck, chest, abdomen, and pelvis and any other disease sites within 28 days before the first dose of study drug. Additionally, a baseline PET-CT scan will be performed within 60 days before first dose of study drug. Bone marrow aspirate/biopsy (including IHC) within 60 days before first dose of study drug is also required per clinical guidelines. Information on extranodal involvement will also be recorded. No anti-cancer treatment other than study treatment can be implemented between the earliest date of pretreatment scans or bone marrow biopsy and the treatment of study drug.

Tumor assessments include physical exam, radiographic examination, endoscopy, and bone marrow assessment. Bone marrow assessments are required for confirmation of CR for subjects who have disease involvement at screening per clinical guidelines (see CSP Section 1.1). Likewise, endoscopy is required to confirm CR for any subjects with a documented history of gastrointestinal involvement. During treatment, CT scans with contrast (unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites will be performed for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6; and then every 3 cycles (12 weeks) thereafter or more frequently at investigator discretion, until disease progression, regardless of whether the subject receives a new anticancer therapy. During treatment, PET-CT scans will be performed at the end of Cycle 2 (± 7 days) and Cycle 6 and are required to confirm CR or as clinically indicated. Subjects with confirmed CR are not required to undergo further PET-CT scans on study unless there is suspicion of progressive disease in CT but cannot be proven, PET-CT may be used at the investigator's discretion.

From the investigator's review of the tumour assessment, the tumour response data will be used to determine each patient's visit response according to Lugano criteria (Cheson 2014). At each visit, patients will be assigned a Lugano criteria visit response of CR, PR, SD or PD, according to PET-CT-Based Response or CT-Based Response. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of not applicable (NA), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Table 2 for the definitions of CR, PR, SD and PD.

Table 2 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic 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 (e.g., 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 the marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra lymphatic 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 x 5 mm as the default value
		When no longer visible, 0 x 0 mm
	At end of treatment, these findings indicate residual disease	For a node >5 x 5 mm, but smaller than the 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

Table 2 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for 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 increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 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 (e.g., 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

Table 2 Response assessment criteria for NHL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = [18F] fluorodeoxyglucose; IHC = immunohistochemistry; GI = gastrointestinal; 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 (e.g., liver, spleen, kidneys, and 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 measureable 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 (e.g., 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 (e.g., 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.

3.1.2. Response assessment criteria for CLL

The iwCLL criteria (modified from Hallek 2018) (see CSP Table 8) will be used to determine each CLL patient's response at each visit. It will also be used to determine if and when a patient has progressed.

For baseline, a CT scan with contrast (MRI should be used if contraindicated) is required to cover the neck, chest, abdomen, and pelvis and any other disease sites (e.g. brain), within 28 days before the first dose of study drug. Spleen and liver size should be recorded in CT

measurement. Additionally, bone marrow aspiration and biopsy within 3 months before first dose of study drug is required. Physical exam (especially lymph node and organomegaly), B symptoms, blood counts with differential and other clinical information should be recorded in the eCRF at the baseline. PET-CT is not required, but if performed within 60 days before the study treatment, should be recorded in eCRF.

Radiologic tumour assessment will be performed every 12 weeks (± 7 days) with the first on-treatment radiologic assessment occurring on Cycle 4 Day 1, the second on treatment scan on Cycle 7 Day 1, and so on through Cycle 25, and then every 24 weeks (± 7 days) thereafter. For subjects who achieve a response (CR, CRi, PR, or nPR), CT must be performed for response confirmation in 12 weeks (±7 days) after the initial response imaging assessment, and then every 24 weeks (±7 days) thereafter.

From the investigator's review of the tumour assessment, the tumour response data will be used to determine each patient's visit response according to iwCLL criteria (Hallek 2018). At each visit, patients will be assigned a iwCLL criteria visit response of CR, CRi, nPR , PR, PRL, SD or PD. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of not applicable (NA), (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Table 3 for the definitions of CR, CRi, nPR, PR, PRL, SD or PD.

Table 3 Response Assessment Criteria for CLL (modified from Hallek 2018) – iwCLL Criteria **

Group	Parameter	CR *	PR #	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)[a]	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size[b]	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of -49% to +49%
B	Platelet count	≥100,000/μL	≥100,000/μL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CL	Change of -49% to +49%

	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease >2 g/dL
	Marrow	Normocelluar, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

Abbreviations: CLL=chronic lymphocytic leukemia; CR=complete response; CT=computed tomography; PD=progressive disease; PR=partial response; SD=stable disease.

Note: CR, complete remission: all of the criteria have to be met; PR, partial response: for a PR at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal. If only one parameter of both groups A and B is abnormal prior to therapy, only 1 needs to improve. PD, progressive disease: at least one of the above criteria of group A or group B has to be met; SD, stable disease: all of the above criteria have to be met. Constitutional symptoms alone do not define PD.

a. Sum of the products of 6 or less lymph nodes (as evaluated by CT scans and physical examination in clinical trials, or by physical examination in general practice).

b. Spleen size is considered normal if <13 cm. There is not firmly established, international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

* CRi (CR with incomplete bone marrow recovery) refers to subjects who fulfill all the criteria for a CR (including the bone marrow examinations), but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically, should be considered to have "nodular PR" (nPR). Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, lymphocytes other than CLL cells, or CLL cells. If the nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met.

PRL (partial response with lymphocytosis): presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the PR criteria for platelets or hemoglobin have to be met.

**patients who previously assessed based on Hallek 2008 per initial protocol should be re-evaluated based on Hallek 2018 if possible.

For a detailed description of the response parameters see Hallek 2018.

3.1.2.1. Additional requirement for CLL response Assessment

Laboratory tests

Hematology will be evaluated at the central laboratory and will include a complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and ALC. Any missing central laboratory blood samples should be redrawn as soon as possible. In the event that the missing central laboratory sample is unrecoverable, local laboratory results will be collected, if available, and entered in the clinical database.

B-Symptoms

B-symptoms is part of tumor response assessment for CLL subjects per Hallek 2018. B-symptoms should not be reported as AEs. Worsening is generally considered a symptom (but not an objective criterion) of progression.

B-symptoms are constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months
- Significant fatigue (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities)
- Fevers >100.5°F or 38.0°C for ≥2 weeks without other evidence of infection
- Night sweats for >1 month without evidence of infection

3.1.3. Blinded independent central review (BICR)

A central imaging service (BICR) provided by a third-party vendor company will be used to provide independent radiologic assessments for the purposes of the efficacy endpoint. The assessment results from BICR will not be reported back to the site. De-identified copies of all radiology results may be requested by the sponsor. Subjects who have signs and symptoms of progression outside of the scheduled assessment should be evaluated by the investigator with a physical exam and laboratory assessments to determine if disease progression is present. Any suspected case of disease progression should be confirmed with a CT and should be reported to the sponsor or designee. Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. In addition, when clinically appropriate, based on investigator-perceived risk/benefit assessment, a subject may continue treatment until objective progression is confirmed. New anticancer therapy should be withheld if clinically appropriate in the absence of objectively confirmed progressive disease.

The CT portion of a PET-CT may be submitted in lieu of a dedicated CT; however, certain radiologic requirements are needed for acceptance, provided it is of diagnostic quality. Magnetic resonance imaging (MRI) may be used for subjects who are either allergic to CT contrast media or have renal insufficiency that per institutional guidelines restricts the use of CT contrast media.

Further details of the BICR will be documented in the BICR Charter.

3.2. Phase 1

3.2.1. Efficacy variables

Efficacy will be assessed in terms of tumor response by best overall response (BOR). For R/R NHL patients, these will be described by number of patients with tumor response (CR, PR,

SD, PD) according to the Lugano classification for R/R NHL (Cheson 2014). For R/R CLL patients these will be the number of patients with tumor response (CR, CRi, nPR, PR, PRL, SD, PD) according to the iwCLL 2018 criteria (Hallek 2018). Appropriate descriptive summaries of these data will be presented as described in Section 3.2.2.

3.2.1.1. Best overall response (BOR)

Best overall response is the best visit response a patient has had following first dose date, but prior to starting any subsequent anticancer therapy up to and including progression or the last evaluable assessment in the absence of progression. To determine the BOR, the following order is used:

- For R/R NHL patients: CR > PR > SD > PD > NE.
- For R/R CLL patients: CR > CRi > nPR > PR > PRL > SD > PD > NE.

Patients will be assigned a BOR of NE (Non-Evaluable) if all post-baseline responses are either missing (not documented) or documented as NA (Not Applicable) or Unknown.

3.2.2. Safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, physical examinations, vital signs, ECG and ECOG performance status. These will be collected for all subjects. Appropriate descriptive summaries of these data will be presented as described in Section 4.2.3. All summaries will be presented by the safety analysis set.

3.2.2.1. Adverse events

Adverse Events and SAEs will be collected from time of signature of informed consent form until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever comes first).

The Medical Dictionary for Regulatory Activities (MedDRA) (MedDRA version 24.0 or later) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE, latest available version).

Treatment-emergent AEs are defined as those events that occur or worsen on or after the first dose of study drug, through the treatment phase, and until 30 days after the last dose of study treatment or the start of new anticancer therapy (whichever occurs first). AEs occurring before the first administration of IP but increase in severity or frequency on or after administration of IP will be considered as treatment-emergent as well. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

AEs of special interest (AESIs)

The following events are adverse events of special interest (AESIs) for all subjects in this study and must be reported to the sponsor expeditiously irrespective of regulatory seriousness criteria or causality:

Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.) as defined in Appendix 8.1.1..

Events of Clinical Interest

Some clinical concepts (including some selected individual preferred terms and higher-level terms) have been considered "Events of Clinical Interest" (ECIs) to the acalabrutinib program. ECIs include cardiac events, cytopenias (anemian, leukopenia and thrombocytopenia), hemorrhage, hepatotoxicity, hypertension, infections, intestinal lung disease/pneumonitis, tumor lysis syndrome, and secondary primary malignancies.

These ECIs have been identified as a list of categories provided by the patient safety team. ECIs are defined in Appendix 8.1 and search strategy for narratives are defined in Appendix 8.2.

Other categories may be added as necessary or existing terms may be merged. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of clinical interest and identified which higher-level terms and which preferred terms contribute to each ECI. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories.

3.2.2.2. Exposure and dose interruptions/delay

Total exposure (i.e. duration of treatment or intended exposure), actual exposure, dose withholding and dose reduction will be defined as follows:

- Total (or intended) exposure = min(last dose date where dose > 0 [units], date of death, date of DCO) – first dose date +1
- Actual exposure = intended exposure – number of days where the patient has not taken any study treatment
- Dose withholding is defined as missing doses for ≥ 7 consecutive days.
- Dose reduction is defined as taking a lower dose (100 mg daily) for ≥ 3 consecutive days.

The calculation of actual exposure considers only full days where the patient did not take any study treatment as defined above. It makes no adjustment for reduced dosing frequency, taking lower doses, or any other dose modifications that may have occurred.

Patients who permanently discontinue during a dose interruption

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC will be used in the programming. *See further Appendix 8.2.*

3.2.2.3. Dose intensity

See Appendix 8.3 for example RDI calculations.

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity (RDI) will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the or the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule.

- The average daily dose is defined as the ratio of actual cumulative dose (d) and the actual duration of exposure.

3.2.2.4. Laboratory data

Clinical safety laboratory assessment is included in Table 4 and specified into the CSP SoA for the timing and frequency.

The clinical chemistry, hematology (see paragraphs below for specific requirements for CLL subjects in Phase 2 – cohort B), pregnancy test, coagulation, urinalysis, hepatitis, HIV and serum immunoglobulin levels analyses will be performed locally at the visits as indicated in the CSP SoA (see Table 1, Table 2 and Table 3), therefore sample volumes may vary according to local practice. If screening assessment clinical chemistry, hematology, coagulation and urinalysis are performed within 5 days prior to the baseline visit (i.e. first dose day: Phase 1 portion- at Cycle 0 Day 1; Phase 2 portion- at Cycle 1 Day 1), they do not need to be repeated at the baseline visit. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56) will be performed at the central laboratory, samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Table 4 Laboratory variables

Clinical Chemistry [a]	
Calcium	Urea or blood urea nitrogen
Chloride	Uric acid
Magnesium	Creatinine
Phosphate/Phosphorus	Total bilirubin
Potassium	Glucose
Sodium	Albumin
AST	Total protein
ALT	Triglycerides
Alkaline phosphatase (ALP)	Cholesterol

Gamma glutamyl transferase (GGT)	Lactate dehydrogenase (LDH)
Hematology [b]	
White blood cell (WBC) count with differential	Platelet count
Red blood cell (RBC) count	Absolute neutrophil count (ANC)
Hematocrit	Absolute lymphocyte count (ALC)
Hemoglobin	
Urinalysis	
pH	Bilirubin
Specific gravity	Protein
Glucose	Ketones
Blood	
Pregnancy Test (females of childbearing potential only)	
Urine human chorionic gonadotropin (hCG) or Serum βhCG	
Hepatitis B and C Testing [c]	
HBsAg	Hepatitis B surface antibody (HBsAb)
Anti-HBc	Hepatitis C (hepatitis C virus [HCV]) antibody
Hepatitis B PCR (clinically indicated)	Hepatitis C PCR (clinically indicated)
Coagulation	
Coagulation tests: prothrombin time (PT)	Activated partial thromboplastin time (aPTT)
Fibrinogen	
Other Tests	
T/B/NK Cell Count	Serum immunoglobulin levels
HIV antibody	β2-microglobulin [d]
Cytogenetics and FISH Panel [d,e]	Genetic and molecular prognostic molecules[d,f]

a. In case a subject shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN please refer to CSP Appendix D. 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

b. Hematology will be evaluated at the central laboratory for CLL subjects in Phase 2 – cohort B.

c. Hepatitis serology testing must include HBsAg, HBsAb, anti-HBc and hepatitis C (HCV) antibody. In addition, any subjects testing positive for anti-HBc must have quantitative PCR testing for HBV DNA during screening and monthly basis from Cycle 2 through 19. After Cycle 19, monitoring will occur every 3 months. HBV monitor should continue until 12 months after last dose of study drug (see CSP Table 1, Table 2, Table 3 and exclusion criterion #7). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Since IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels). Refer to CSP Table 1, Table 2 and Table 3 regarding monitoring of subjects who are anti-HBc positive or who have a known history of HBV.

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening. No further testing is necessary if the PCR results are negative at screening.

d. These tests will be performed at the central laboratory and for CLL subjects in cohort B only.

e. Cytogenetics and FISH Panel include 17p del, 13q del, trisomy 12, 11q del by FISH and stimulated karyotyping.

f. Genetic and molecular prognostic molecules panel include, but is not limited to, sequencing of p53 mutations, immunoglobulin heavy-chain variable (IGHV) mutational status.

3.2.2.5. Physical examinations

The physical examination includes height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal, nervous, lymphatic system, and general appearance. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Physical examination will be performed at timelines as specified in the SoA.

3.2.2.6. Vital signs

Vital signs (Blood pressure, pulse rate, and body temperature) will be assessed after at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

3.2.2.7. ECG

Twelve-lead ECG will be obtained as outlined in the SoA (see CSP Section 1.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

3.2.2.8. ECOG performance status

ECOG performance status will be assessed at screening, prior to the first dose of study treatment and at all visits thereafter according to ECOG criteria as follows:

Grade	ECOG

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

3.2.3. Pharmacokinetic variables

Pharmacokinetic analysis of the plasma concentration data for acalabrutinib and a metabolite (ACP-5862) will be performed by Covance (Contract Research Organization) on behalf of AstraZeneca.

In Phase 1 portion, venous blood samples for determination of concentrations of acalabrutinib and its metabolite (ACP-5862) in plasma will be taken at the times presented in Table 11 and Table 12 of CSP.

Where possible, the following PK parameters will be estimated using non-compartmental method with plasma concentration data of acalabrutinib and a metabolite (ACP-5862) on Cycle 0 Day 1 and Cycle 1 Day 8 of Phase 1:

- Maximum observed plasma drug concentration (Cmax)
- Time to reach maximum observed drug concentration (tmax)
- Terminal elimination rate constant (λ_Z)
- Half-life associated with terminal slope (λz) of a semilogarithmic concentration-time curve ($t½\lambda z$)
- Area under the plasma concentration-time curve from zero to 12 hours (AUC0-12)
- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration (AUClast)
- Area under the plasma concentration-time curve from zero to infinity (AUCinf)
- Apparent total body clearance of drug from plasma after extravascular administration (CL/F)
- Volume of distribution (apparent) following extravascular administration (based on terminal phase) (V_Z/F)

- Accumulation ratio for AUC calculated as AUCτ (steady state)/AUCτ (first dose) and denoted by Rac AUC
- Accumulation ratio calculated as Cmax (steady state)/Cmax (first dose) and denoted by Rac Cmax
- Temporal change parameter (TCP) calculated as AUCτ (steady state)/AUCinf (first dose)
- Metabolite: Parent ratio for AUC calculated as AUC (metabolite)/AUC (parent)
- Metabolite: Parent ratio for Cmax calculated as Cmax (metabolite)/Cmax (parent)
- Diagnostic parameters:
    - λzN: number of data points used for λz determination
    - λz lower: lower (earlier) t used for λz determination
    - λz upper: upper (later) t used for λz determination
    - λz span ratio: time period over which λz was determined as ratio of t½λz
    - Rsq: statistical measure of fit for the regression used for λz determination
    - Rsq adj.: statistical measure of fit for the regression used for λz determination adjusted for the number of used data points
    - AUCextr: extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf
    - Tlast: time of last observed (quantifiable) concentration

The Cmax and tmax will be determined by inspection of the concentration-time profiles. Where possible the λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data, and the t½λz will be calculated as ln2/λz. The AUC_{0-12}, and AUClast will be calculated using the linear/log trapezoidal rule (i.e. "linear-up-log-down": the linear trapezoidal rule is used any time that the concentration data is increasing, and the logarithmic trapezoidal rule is used any time that the concentration data is decreasing). Where appropriate, the AUClast will be extrapolated to infinity using λz to obtain AUCinf. The CL/F will be determined from the ratio of dose/AUC. The Vz/F will be determined from the ratio of CL/F/λz. The Rac AUC and Rac Cmax will be calculated as the ratio of the AUCτ or Cmax on Cycle 1 Day 8 and Cycle 0 Day 1, respectively. The TCP will be assessed by the calculation of the ratio of AUCτ on Cycle 1 Day 8 and AUCinf on Cycle 0 Day 1. The Metabolite: Parent ratio parameters will be calculated after molar conversion.

3.3. Phase 2

3.3.1. Efficacy variables

3.3.1.1. Best overall response (BOR)

Best overall response is the best visit response a patient has had following first dose date, but prior to starting any subsequent anticancer therapy up to and including progression or the last evaluable assessment in the absence of progression, assessed by BICR. To determine the BOR, the following order is used:

- For R/R MCL patients: CR > PR > SD > PD > NE.
- For R/R CLL patients: CR > CRi > nPR > PR > PRL > SD > PD > NE.

Patients will be assigned a BOR of NE (Non-Evaluable) if all post-baseline responses are either missing (not documented) or documented as NA (Not Applicable) or Unknown.

3.3.1.2. Overall response rate (ORR) as assessed by BIRC

For R/R MCL subjects, ORR will be defined as the proportion of subjects who achieve either a CR or PR as BOR in the tumor response analysis set, according to the Lugano Classification for NHL (Cheson 2014), as assessed by BICR.

For R/R CLL subjects, ORR will be defined as the proportion of subjects who achieve a CR, CRi, nPR, PR, as BOR in the tumor response analysis set, according to iwCLL 2018 criteria (Hallek 2018) as assessed by BICR.

Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the ORR.

ORR plus patients with a best overall response of PRL will also be assessed, denoted as ORR+PRL.

3.3.1.3. Duration of Response (DoR) as assessed by BIRC

DoR is defined as the interval from the first documentation of objective response (PR or better) mentioned above to the earlier of the first documentation of objective disease progression by the BICR or death from any cause.

Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy.

- For BICR assessments, the date of progression will be determined based on the **earliest** of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of the reviewer who read baseline first if there is no adjudication for BICR data.

- For investigator assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression.

- For both BICR and investigator assessments, when censoring a patient for DoR the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

Table 5 Censoring rules for DoR

Assessment	Outcome	Date of progression or censoring
Documented PD between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of death
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment
Documented PD or death after 2 or more consecutively missed visits following the first documentation of objective response	Censored	Date of last adequate disease assessment before the consecutively missed visits

PD = progressive disease

3.3.1.4. Progression-free survival (PFS) as assessed by BIRC

PFS is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective disease progression by the BICR or death from any cause.

Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy. For patients without an adequate post-baseline disease assessment or no baseline assessments, PFS will be censored on the date of randomization unless they die within 2 visits of baseline.

Table 6 Censoring rules for PFS

Assessment	Outcome	Date of progression or censoring
Death before first disease assessment	Event	Date of death
Documented PD between scheduled visits on or before receiving subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression
Death without documented PD and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of death
No baseline tumor assessments and it's not known to have died in 2 consecutive visits of baseline	Censored	Date of first dose
No adequate post-baseline assessment and it's not known to have died in 2 consecutive visits of baseline	Censored	Date of first dose
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment
No documented PD or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer treatment
Documented PD or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff
No documented PD or death at the time of data cutoff and subject not received subsequent anticancer therapy or subsequent anticancer therapy started after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff
Withdrew consent without documented PD or death	Censored	Date of last adequate disease assessment
Lost to follow-up without documented PD or death	Censored	Date of last adequate disease assessment
Documented PD or death after 2 or more consecutively missed visits	Censored	Date of last adequate disease assessment before the consecutively missed visits

PD = progressive disease

3.3.1.5. Time to response (TTR) as assessed by BIRC

TTR will be analyzed for subjects with objective response (PR or better) and is defined as the interval between the date of first dose and the date of initial documentation of a response. Time to initial response as well as time to best response (in the order of CR > PR for r/r MCL and CR > CRi > nPR > PR for r/r CLL) will be derived.

3.3.1.6. Investigator-assessed endpoints (ORR, DoR, PFS and TTR)

Definition of ORR, DoR, PFS and TTR by the investigator assessment will follow BICR assessed endpoints as above.

3.3.1.7. Overall survival (OS)

OS is defined as the interval from the start of acalabrutinib therapy to death from any cause. Subjects who are known to be alive as of their last known status will be censored at their last date known to be alive.

Table 7 Censoring rules for OS

Assessment	Outcome	Date of progression or censoring
Death on or before data cutoff	Event	Date of death
Alive before data cutoff	Censored	Date subject last known to be alive
Death after data cutoff	Censored	Date of data cutoff
Alive on or after data cutoff	Censored	Date of data cutoff
Withdrew consent prior to data cutoff	Censored	Date of discontinuation from study participation as reported on study exit CRF
Lost to follow-up prior to data cutoff	Censored	Date subject last known to be alive

3.3.1.8. Time to Next Treatment (TTNT, for R/R CLL only)

TTNT is defined as the interval from the start of acalabrutinib therapy to institution of non-protocol specified anti-cancer treatment for CLL or death due to any cause, whichever comes first. Data from surviving subjects who do not receive any non-protocol specified treatment will be censored at the last time that lack of non-protocol specified treatment was objectively documented.

Table 8 Censoring rules for TTNT

Assessment	Outcome	Date of progression or censoring
Next treatment or death on or before data cutoff	Event	Earliest date of next treatment or death
Do not receive next treatment and alive on or before data cutoff	Censored	Last time that lack of non-protocol specified treatment
Next treatment and alive after data cutoff	Censored	Date of data cutoff
Next treatment and death after data cutoff	Censored	Date of data cutoff

Table 8 Censoring rules for TTNT

Assessment	Outcome	Date of progression or censoring
Do not receive next treatment at any time and death after data cutoff	Censored	Date of data cutoff
Do not receive next treatment at any time and alive after data cutoff	Censored	Date of data cutoff
Withdrew consent without next treatment prior to data cutoff	Censored	Date of discontinuation from study participation as reported on study exit CRF
Lost to follow-up without next treatment prior to data cutoff	Censored	Last time that lack of non-protocol specified treatment

3.3.1.9. Minimum Residual Disease Rate (for Phase 2 R/R CLL only)

Minimal residual disease negative rate is defined as the proportion of subjects with MRD-negativity measured in the peripheral blood by flow cytometry (defined as <1 CLL cell per 10,000 leukocytes) by central lab.

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that PR, CR or CRi has been achieved, a peripheral blood by flow cytometry sample to evaluate MRD should be done between 8-12 weeks from the time of supportive clinical assessments including CT imaging of suspected PR, CR or CRi.

A peripheral blood sample testing for minimal residual disease (MRD) will be done at screening and end of treatment visit or if not taken at the EoT visit, then it can be drawn at SFU visit.

3.3.2. Safety variables

Please refer section 3.2.2 as same safety variables will be applied for Phase 2. As for clinical laboratory assessments, some additional laboratory tests will be required for CLL subjects in phase 2 – cohort B only, more detailed information please refer Table 4.

3.3.3. Pharmacokinetic variables

In Phase 2 portion, the schedule of sparse PK sampling for determination of acalabrutinib plasma concentration is presented in Table 13 of CSP.

4. ANALYSIS METHODS

4.1. General principles

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.

- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. While please refer section 4.2.6 for precision and rounding rules for pharmacokinetic data.

- For categorical data, percentages will be rounded to 1 decimal place.

- SAS® version 9.1 *(as a minimum)* will be used for all analyses.

In general, for all endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100. (If applicable add: For any variable subjected to log transformation, the change from baseline calculated and summarized on the log scale will be back-transformed and presented as a 'baseline scaled ratio' (BSR). Percentage change will then be calculated as (BSR - 1) x 100.)

Data will be presented separately for three cohorts:

- Phase 1 patients
- R/R MCL patients (Phase 1 and Phase 2 combined)
- R/R CLL patients (Phase 2 only)

Demographic data, exposure and safety data will be analyzed based on safety analysis set. Pharmacokinetics will be analyzed based on PK analysis set. Efficacy analyses will be analyzed on tumor response analysis set.

The method for handling missing data is described in the definition for each of the endpoints. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date, the algorithm in Appendix 8.4 will be used.

4.2. Analysis methods

4.2.1. Data cut-offs

There are two planned analyses for all subjects of Phase 1 portion and cohort A of Phase 2 portion.

The data cut-off for the 1st analysis will take place when both of the following two conditions are met

- Approximately 1 month after cycle 1 day 1 of the last subject in Phase 1 to allow required PK samplings at cycle 0 and cycle 1 are collected.
- Approximately 6 months after last R/R MCL subjects across both Phase 1 and Phase 2 to allow a minimum of two tumor assessments after first dose.

A Clinical Study Report will be prepared to summarize PK, safety and efficacy data for Phase 1 portion and/or cohort A of Phase 2 portion. R/R MCL subjects in Phase 1, if applicable, will be combined together with the subjects in cohort A of Phase 2 portion for MCL analysis.

The data cut-off for the 2nd analysis will take place approximately 14 months after last subject enrolled in both Phase 1 and cohort A of Phase 2. A Clinical Study Report Addendum including all subjects of Phase 1 portion and/or cohort A of Phase 2 portion will be prepared at that time.

Selected safety summaries might be generated for R/R MCL subjects across Phase 1 and Phase 2.

There are three planned analyses for R/R CLL subjects of cohort B of Phase 2 portion.

The data cut-off for the 1st analysis will take place when approximately 6 months after last R/R CLL subjects enrolled in Phase 2. A Clinical Study Report will be prepared to summarize efficacy, safety and PK data for cohort B of Phase 2 portion. Efficacy analysis of tumor response in R/R CLL will only be applied for R/R CLL subjects in Phase 2. Tumor response of R/R CLL subjects in Phase 1 may be listed separately.

The data cut-off for 2nd analysis will take place when approximately 12 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

The data cut-off for 3rd analysis will take place approximately 24 months after last R/R CLL subject enrolled in Phase 2. A Clinical Study Report Addendum including R/R CLL subjects of cohort B of Phase 2 portion will be prepared at that time.

4.2.2. Efficacy analyses

4.2.2.1. Best overall response (BOR)

Number and percentage of patients within a particular best overall response (BOR) category will be provided for the following patients in separate tables: R/R NHL phase 1 patients, R/R CLL phase 1 patients, R/R MCL patients (phase 1 and phase 2 combined) and R/R CLL patients (phase 2 only). In addition, numbers and percentages of BOR by disease group (MCL, non-GCB DLBCL, FL, SLL) for phase 1 R/R NHL patients as well as for phase 2 R/R CLL patients with del 17p will be presented in separate additional tables.

For R/R NHL(MCL,non-GCB DLBCL, FL, SLL) patients, the response categories are (CR, PR, SD, PD) and assessments are based on the Lugano criteria. For R/R CLL patients, these are (CR, CRi, nPR, PR, PRL, SD, PD) and assessments are based on iwCLL 2018 criteria. For R/R NHL phase 1 and R/R CLL phase 1, tables with responses based on investigator assessments will be presented. For R/R MCL patients (phase 1 and phase 2 combined) and R/R CLL patients (phase 2) separate tables for assessments by investigator and BICR will be created.

For R/R NHL phase 1 and R/R CLL phase 1, investigator-assessed BOR will be listed separately. For R/R MCL patients (phase 1 and phase 2 combined) and R/R CLL patients (phase 2) separate listings with investigator-assessed BOR and BICR-assessed BOR will be presented.

The analysis will be based on the tumor response set.

4.2.2.2. Overall response rate (ORR)

Primary analysis of BICR-assessed ORR will be conducted on the tumor response analysis set for MCL patients (phase 1 and phase 2 combined) and R/R CLL patients (phase 2) separately. ORR and the corresponding 95% two-sided CI of ORR will be presented based on Clopper-Pearson exact method. BICR–assessed ORR+PRL and the corresponding 95% two-sided Clopper-Peason CI will also be presented.

.For MCL patients (phase 1 and phase 2 combined), maximum percentage changes from baseline in the sum of product diameters (SPD) will be presented using waterfall plots (tumor response marked with different colors) based on BICR assessments.

Analysis of investigator-assessed ORR, ORR+PRL and SPD will be conducted on the tumor response analysis set using same statistical methods. The concordance between investigator-assessed and BIRC-assessed ORR as well as CR and PR rates will be summarized for MCL cohort. The concordance between investigator-assessed and BIRC-assessed ORR, CR or CRi rate and ORR+PRL rate will be summarized for CLL cohort.

Subgroup analysis

Additionally, subgroup analysis following the categories as below will be performed where deemed appropriate, these will be summarized and presented on a forest plot including the BICR-assessed ORR and 95% CI.

- Age at enrolment (<65 versus >=65; <75 versus >=75)
- Sex (male versus female)
- ECOG (0 versus 1 versus >=2)
- Bulky disease (longest diameter of lymph node <5 cm vs. >=5 cm and <10 cm vs >=10 cm at baseline)
- Number of previous lines (1 versus 2 versus >=3)
- Extranodal disease (yes versus no) – MCL only
- Bone marrow involvement (yes versus no) – MCL only
- Gastrointestinal disease (yes versus no) – MCL only
- Simplified MCL international prognostic index (MIPI) (low risk [0-3] vs intermediate risk [4-5] vs high risk [6-11]) – MCL only
- Refractory disease at baseline (yes versus no)
- Ann Arbor lymphoma staging (1-3 versus 4) -MCL only
- Rai staging at baseline (0-II versus III-IV) - Phase 2 cohort B only
- β2-microglobulin at baseline (≤3.5 mg/L vs. >3.5 mg/L) – Phase 2 cohort B only
- IGHV mutation (mutated versus unmutated) – Phase 2 cohort B only
- 17p deletion (yes versus no) – Phase 2 cohort B only
- 11q deletion (yes versus no) – Phase 2 cohort B only
- TP53 mutation (mutated versus unmutated) - Phase 2 cohort B only

In addition, same the subgroup analysis will be presented for the investigator assessed ORR.

4.2.2.3. Tumor response by visit

Time windows will be used to ensure tumor response data recorded at any time point has the potential to be summarized, for details refer to section 4.2.3.1.

Both BICR and investigator tumor response data will be summarized by visit using time windows for the phase 2 R/R CLL cohort only. Investigator-assessed tumor response for R/R NHL phase 1 patients, R/R CLL phase 1 patients, R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients at each timepoint will be presented in listings and swimmer plots. BICR-assessed tumor response by timepoint will be presented in listings and swimmer plots for R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients.

4.2.2.4. Duration of response (DoR)

The analysis of BICR-assessed DoR will be estimated using the Kaplan-Meier (KM) methods will be performed on R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients separately. KM estimates will be calculated for event time quartiles (including median, Q1 and Q3), and event-free rates will be calculated at selected time points (i.e. 6 months, 12 months, 18 months).

In addition, type of event (i.e. death, PD) and the reason for censoring (i.e. data cutoff, lost to follow-up, subsequent anticancer therapy) will be summarized in the same table. Please refer Table 5 for censoring rules.

Kaplan-Meier plot for duration of response will be created accordingly. In addition, Kaplan-Meier plot for duration of response by best overall response (PR and CR) will be developed in a separated plot.

The analysis will be performed on the tumor response set.

4.2.2.5. Progression-free survival (PFS)

The analysis of BICR-assessed PFS will be performed for R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients separately and in the same way as DoR. Please refer Table 6 for censoring rules.

4.2.2.6. Time to response (TTR)

BICR-assessed time to initial response and time to best response will be summarized separately using descriptive statistics for R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients on the tumor response set

4.2.2.7. Investigator-assessed endpoints (DoR, PFS and TTR)

The same analysis methods for BICR-assessed endpoints (DoR, PFS, and TTR) will be applied to investigator-assessed endpoints.

4.2.2.8. Overall survival (OS)

The analysis of OS will be performed in the same way as DoR. Please refer Table 7 for censoring rules.

4.2.2.9. Time to Next Treatment (TTNT, cohort B only)

Time to next treatment (for R/R CLL only) will be performed in the same way as DoR. Please refer Table 8 for censoring rules.

4.2.2.10. Minimum Residual Disease Rate (MRD, cohort B only)

MRD negativity rate will be summarized for phase 2 R/R CLL subjects only.

4.2.3. Safety analyses

4.2.3.1. General considerations for safety

The analysis will be performed separately for all three cohorts: all phase 1 patients, R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients except where it is mentioned otherwise.

Time windows will be defined for any presentations that summarize values by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window will be based on the actual date and not the intended date of the visit.

- All unscheduled visit data have the potential to be included in the summaries.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. For example, the visit windows for vital signs data (with 1 weeks between scheduled assessments) are:

    - Day 8, visit window 2 – 11
    - Day 15, visit window 12 – 18
    - Day 22, visit window 19 – 25
    - Day 28, visit window 26 – 32

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).

- Listings should display all values contributing to a time point for a patient.

- For visit based summaries

    – If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarized, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date

- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

- Baseline for safety assessments will generally be the last value obtained prior to the first dose of study medication. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, study day will be calculated in relation to date of first treatment.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or > x (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

For missing date of initial diagnosis and start dates for AEs, medical history and concomitant medications/procedures, the following will be applied:

- Missing day: Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.
- Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs, medical history and concomitant medications/procedures, the following will be applied:

- Missing day: Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date.
- Missing day and month: Impute 31st December unless year is the same as last dose date then impute last dose date.
- Completely missing: If an AE, MH/medication has a completely missing end date then it will be treated as ongoing. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

For partial subsequent anti-cancer therapy dates, the following will be applied:

- Missing day: If the month is the same as treatment end date then impute to the day after treatment, otherwise first day of the month.

- Missing day and month: If year is the same as treatment end date then impute to the day after treatment, otherwise 1st January of the same year as anti-cancer therapy date.

4.2.3.2. Exposure and Compliance

Descriptive statistics will be produced to describe the exposure to acalabrutinib specified in section 3.2.2.2 for the safety analysis set:

- Total treatment duration (months)
- Number (%) of patients with total treatment duration
  - ≤ 3 months
  - > 3 months to ≤ 6 months
  - > 6 to ≤ 12 months
  - >12 to ≤ 24 months
  - >24 months
- Actual treatment duration (months)
- Actual cumulative dose
- Average daily dose
- Relative dose intensities (%)
- Number of dose withholdings and number (%) of patients with dose withholdings
- Number of dose reductions and number of (%) of patients with dose reductions

4.2.3.3. Adverse events

Treatment-emergent AEs as defined in section 3.2.2.1 will be used for the reporting of the AE summary tables. Any events that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings. Moreover, AEs occurring more than 30 days after discontinuation of study treatment and any AE occurring before giving the study treatment will be included in the data listings as well.

An overall summary of the number and percentage of patients in each of the aforementioned categories will be presented for the following:

- All TEAEs
- All drug-related TEAEs
- All TEAEs with CTCAE grade ≥3
- All drug-related TEAEs with CTCAE grade ≥3
- All serious TEAEs

- All drug-related serious TEAEs
- TEAEs leading to treatment discontinuation
- Drug-related TEAEs leading to treatment discontinuation
- TEAEs leading to dose interruption and modification
- TEAEs leading to death
- Drug-related TEAEs leading to death

All AEs will be listed.

A separate listing for adverse events for enrolled but not assigned to treatment patients and for patients who were not exposed to treatment will be created.

4.2.3.3.1. TEAEs and drug-related TEAEs

Treatment-emergent AEs are defined in section 3.2.2.1.TEAEs and drug-related TEAEs will be summarized by system organ class and preferred terms, by CTCAE toxicity grade separately. In addition, TEAEs with CTCAE grade ≥3 and drug-related TEAEs with CTCAE grade ≥3 will be summarized separately in same manner. Summaries of the TEAEs mentioned above will also be provided by preferred term alone.

4.2.3.3.2. Serious TEAEs and drug-related serious TEAEs

Serious TEAEs and drug-related serious TEAEs will be summarized by system organ class and preferred terms and by CTCAE toxicity grade separately. In addition, summaries of serious TEAEs by preferred term alone will be provided.

4.2.3.3.3. TEAEs and drug-related TEAEs leading to treatment discontinuation

TEAEs and drug-related TEAEs leading to treatment discontinuation will be summarized by system organ class and preferred terms and by CTCAE toxicity grade separately. In addition, summaries of TEAEs and drug-related TAEs leading to discontinuation by preferred term alone will be provided.

4.2.3.3.4. TEAEs leading to dose interruption and modification

TEAEs leading to dose interruption and dose modification (reduced) will be summarized by system organ class and preferred terms and by CTCAE toxicity grade. In addition, summaries of TEAEs leading to dose interruption and modification by preferred term alone will be provided.

4.2.3.3.5. TEAEs leading to death and drug-related TEAEs leading to death

TEAEs leading to death and drug-related TEAEs leading to death will be summarized by system organ class, preferred terms and CTCAE toxicity grade separately. In addition, summaries of TEAEs leading to death and drug-related TEAEs leading to death by preferred term alone will be provided.

4.2.3.3.6. Adverse events of special interest (AESI)

AESIs are defined in sections 3.2.2.1. and 8.1.1.

Summaries of the below-mentioned grouped AE categories will include number (%) of patients who have:

- At least one drug-related AESI
- At least one AESI leading to discontinuation of study medication

AESI, drug-related AESI and AESI leading to discontinuation of study medication will be summarized by grouped term and preferred terms in descending order of frequency and by CTCAE toxicity grade separately.

4.2.3.3.7. Events of Clinical Interest (ECI)

ECIs are defined in sections 3.2.2.1 and 8.1.2.

A summary of the number and percentage of patients with treatment-emergent ECIs will be provided by ECI category and ECI subcategory. In addition, for each ECI category, a separate summary table will be displayed with number and percentage of treatment-emergent ECIs by ECI subcategory and Preferred Term.

4.2.3.3.8. Deaths

All deaths and deaths on-treatment or within 30 days of last dose will be summarized. Details of any deaths will be listed for all patients.

4.2.3.4. Laboratory variables

Project-specific reference ranges will be applied for laboratory variables (hematology, clinical chemistry).

Hematology, clinical chemistry, urinalysis, coagulation, T/B/NK Cell Count, Serum Immunoglobulin will be listed individually by patient and suitably summarized. For all laboratory variables, which are included in the version 5.0 of CTCAE, the CTCAE grade will be calculated.

Numerical laboratory data (absolute and change from baseline) will be summarized by scheduled study day using standard summary statistics (mean, standard deviation, minimum, median, maximum, and number of observations) except for urinalysis.

For hematology and clinical chemistry data shift tables will summarize the change from baseline to maximum on-treatment CTCAE grade, the change from baseline to maximum value, and the change from baseline to minimum value .

Number and percentage of patients with treatment-emergent abnormal hematology and clinical chemistry will be presented by parameter and direction (increased/decreased) for grades >= 3 and all grades. To identify potential Hy's Law (see CSP Appendix D for further

details) cases, subjects who have ALT or AST ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN at any time during the study will be flagged in the listings.

Hematological parameters of clinical interest, such as absolute neutrophil count (ANC), hemoglobin, platelets, leukocytes, absolute lymphocyte count (ALC), over time will be plotted for CLL cohort.

A summary of liver function test abnormalities will be provided as follows:

- Number (%) of patients with ALT ≥ 3x to ≤ 5x ULN, > 5x to ≤ 8x ULN, > 8x to ≤ 10x ULN, > 10x to ≤ 20x ULN and > 20x ULN
- Number (%) of patients with AST ≥ 3x to ≤ 5x ULN, > 5x to ≤ 8x ULN, > 8x to ≤ 10x ULN, > 10x to ≤ 20x ULN and > 20x ULN
- Number (%) of patients with ALT or AST ≥ 3x to ≤ 5x ULN, > 5x to ≤ 8x ULN, > 8x to ≤ 10x ULN, > 10x to ≤ 20x ULN and > 20x ULN
- Number (%) of patients with total bilirubin ≥ 2x to ≤ 3x ULN, > 3x to ≤ 5x ULN, > 5x ULN
- Number (%) of patients with potential Hy's Law: (ALT or AST ≥ 3x ULN) and Total bilirubin ≥ 2x ULN.

Figures of liver biochemistry test results over time for patients with elevated ALT or AST, and elevated total bilirubin will be provided.

Scatter plots for maximum treatment-emergent ALT (xULN) vs. maximum treatment-emergent total bilirubun (xULN) and scatter plots for maximum treatment-emergent AST (xULN) vs. maximum treatment-emergent total bilirubun (xULN) will be presented.

For urinalysis a shift table comparing baseline to the maximum value will be presented.

Analysis of Lymphocytosis (rrCLL cohort only)

For all subjects with baseline and any post-baseline ALC measurements, ALC at peak summary will be provided.

Lymphocytosis is defined as an ALC > 5000 cells per microliter and an increase above baseline. The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5,000/μL, whichever occurs first. The following analyses will be conducted for subjects with lymphocytosis in RR CLL cohort: ALC at peak and time to peak ALC for subjects who have lymphocytosis will be summarized with descriptive statistics.

Duration of lymphocytosis is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria.

4.2.3.5. Vital signs

Pulse rate, systolic and diastolic blood pressure, body temperature and weight will be listed by patient and summarized using standard summary statistics for the absolute value and change from baseline at each scheduled study visits.

4.2.3.6. ECOG performance status

ECOG performance status specified in section 3.2.2.8 will be summarized by visits.

4.2.3.7. ECGs

Electrocardiogram details will be listed individually by patient. The only ECG data available will be the QTcF, QT and RR results and the overall evaluations, classified as normal, abnormal not clinically significant and abnormal clinically significant. The actual and change from baseline and assessment time (for QTcF, QT and RR measurements) data will be summarized and the overall evaluations will be using shift tables summarising the change from baseline to last on-treatment observation. Graphical presentations of safety data may be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots may also be considered to investigate trends in parameters compared to baseline.

4.2.4. Demographics and Baseline Characteristics

The analysis will be performed separately for all three cohorts: all phase 1 patients, R/R MCL patients (phase 1 and phase 2 combined) and phase 2 R/R CLL patients except where it is mentioned otherwise.

Descriptive summaries of demographics, baseline characteristics, and baseline disease characteristics will be presented for subjects in the safety analysis set. The following will be summarized for all patients:

- Patient disposition (including screening failures and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis sets
- Demographics (age, age group [< 65, ≥ 65, < 75 and ≥ 75 years], sex, country, race)
- Patient characteristics (Height, Weight, Body Mass Index)
- Medical and surgical histories
- Other baseline characteristics

– Simplified MCL international prognostic index (MIPI) (low risk [0-3] vs intermediate risk [4-5] vs high risk [6-11]) – MCL only

– Ann Arbor staging for lymphoma (1-3 versus 4) - non-CLL only

– RAI staging – CLL only

– Patient disease group (MCL, CLL, non-GCB DLBCL, FL, SLL)

- Previous lines of anti-cancer therapies prior to this study (median, 1, 2, >=3)
- ECOG performance status(0, 1, 2, >=3)
- Alcohol use, categorised (never, current, former)
- Nicotine use, categorised (never, current, former)
- Bulky disease (longest diameter of lymph node >=5 cm, >=10 cm at baseline)
- Extranodal disease (yes versus no) – MCL only
- Bone marrow involvement (yes versus no) – MCL only
- Gastrointestinal disease (yes versus no) – MCL only
- β2-microglobulin at baseline (median, ≤3.5 mg/L, >3.5 mg/L) – Phase 2 cohort B only
- IGHV mutation (mutated versus unmutated) – Phase 2 cohort B only
- 17p deletion (yes versus no) – Phase 2 cohort B only
- 11q deletion (yes versus no) – Phase 2 cohort B only
- TP53 mutation (mutated versus unmutated) - Phase 2 cohort B only
- Refractory disease at baseline

The simplified MIPI score will be derived based on baseline values of 4 prognostic factors: age, and ECOG, lactate dehydrogenase (LDH), white blood cell (WBC). Points will be assigned to each of these factors as presented below and the score will be derived by adding the points for all 4 factors. A score of 0-3 indicates low risk, 4-5 indicates intermediate risk, and 6-11 indicates high risk (Hoster 2008).

Points	Age (year)	ECOG	LDH ULN*	WBC,10^9/L
0	< 50	0-1	<0.67	<6.7
1	50-59	-	0.67-0.99	6.7-9.9
2	60-69	2-4	1.0 – 1.49	1.0-14.9
3	>=70	-	>=1.5	>=15

*LDH relative to upper limit of normal.

Refractory disease is defined as a lack of at least a partial response to the last therapy before study entry (Wang 2013). Refractory disease will be assessed based on the response to the last MCL treatment regimen a subject received prior to study entry and will be categorized as Yes, No. Subject without achieving at least PR or with unknown response to the last treatment regimen prior to study entry will have a value Yes.

4.2.4.1. Disposition

Patient disposition will be summarized and will include the following information:

- Number of patients enrolled to the study (informed consent received), number of patients assigned to treatment, number of patients not assigned to treatment by reason and in total.
- Number and percentage of patients who received treatment and number and percentage of patients who did not receive treatment by reason and in total.
- Number and percentage of patients ongoing treatment (at data cutoff), number and percentage of patients who discontinued treatment (at data cutoff) by reason and in total.
- Number and percentage of patients ongoing study, number and percentage of patients who terminated study by reason and in total.

Patients who discontinued treatment and patients who patients who discontinued study will be listed.The number and percentage of subjects excluded from each analysis set will be presented in a summary table.

4.2.4.2. Protocol deviations

All the important protocol deviations will be summarized and listed for all patients in the safety analysis set. All protocol deviations, including non-important protocol deviations, will be listed.

4.2.4.3. Medical and surgical histories

Medical and surgical histories will be recorded using the medical dictionary for regulatory activities (MedDRA, version 24.0 or later) Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA, and will be summarized descriptively.

4.2.5. Concomitant and other treatments

Information on any treatment within the four weeks prior to initiation of study drug and all concomitant treatments, or objective disease progression (whichever is later), with reasons for the treatment, will be recorded in the eCRF. Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in eCRF.

Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug.

Medications received prior to, concomitantly, or post-treatment will be coded using the WHODRUG Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes. Concomitant medications will be summarized for the safety analysis set by ATC classification codes.

Prior medications, concomitant and post-randomized treatment medications are defined based on imputed start and stop dates as follows:

- Prior medications are those taken prior to study treatment with a start date or stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment, and for 30 days following the last dose of study treatment (and could have started prior to or during treatment).
- Post-treatment medications are those with a start date after the last dose date of study treatment.

The following summaries will be produced:

- Summary of prior anti-cancer therapies
- Summaries of prior medications and prior radiotherapies
- Summaries of concomitant medications Summary of post study treatment anti-cancer therapies
- Summary of post study treatment radiotherapies

All concomitant and other treatment data will be listed.

Missing coding terms should be listed and summarized as "Not coded".

4.2.6. Pharmacokinetic analyses

All PK analyses will be summarized based on the PK analysis set. The data excluded from the PK analysis set will be flagged in subject listing only.

Precision and rounding rules for pharmacokinetic data

For PK concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- Cmax, Cmin – will be presented to the same number of significant figures as received from the bioanalytical laboratory.

- tmax, λz lower and upper time limit – will be presented as received in the data, usually to 2 decimal places

- AUCinf, AUClast, AUC0-12, AUCτ, t½λz, CL/F, Vz/F, Rac ratios, metabolite to parent ratios, Rsq, Rsq adj, λz span ratios – will be presented to 3 significant figures

- λz – will be presented to 4 significant figures

- λz, N – will be presented as an integer (no decimals)

- Tlast - will be presented as received in the data, usually to 2 decimal places

- AUCextr – will be presented to 3 significant figures

For PK concentration data all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameter data the descriptive statistics will be presented according to the following rules:

- Cmax, Cmin, AUCinf, AUClast, AUC0-12, AUCτ, t½λz, CL/F, Vz/F, Rac ratios and metabolite to parent ratios descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

- tmax – all descriptive statistics will be presented as received in the data, usually to 2 decimal places

- λz – all descriptive statistics will be presented to 5 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

Source data shall be used in all derived PK parameter calculations without prior rounding.

Phase 1 portion

Plasma concentrations of acalabrutinib and a metabolite (ACP-5862) will be summarized by nominal sample time. Plasma concentrations at each time point will be summarized by the following summary statistics:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (CV, calculated as $100\sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale)
- Gmean */÷ standard deviation (calculated as exp[μ±s])
- Arithmetic mean
- Standard Deviation (SD)
- Median
- Minimum
- Maximum
- Number of observations

Individual plasma concentrations will be listed by analyte with actual elapsed time (i.e. actual sampling time relative to dosing), actual sampling time (24 hour clock), nominal sampling time (24 hour clock), and the difference between actual and nominal time.

The plasma concentration-time profiles for individual and mean concentrations of acalabrutinib and a metabolite (ACP-5862) will be presented on the linear (linear/linear) scale and on the semi-log (linear/log-linear) scale. Nominal sampling time points relative to dosing

will be used for all mean plots. Actual sampling time points will be used for all individual plots.

Plasma concentrations, that are below the Lower Limit of Quantification (<LLOQ) or if there are missing values (e.g., no result [NR]), will be handled as follows:

- Where there is NR, there will be set to missing.
- If, at a given time point, 50% or less of the plasma concentrations are <LLOQ, all values <LLOQ will be set to the LLOQ/2, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are <LLOQ, the mean, SD, geometric mean and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to <LLOQ.
- If all the concentrations are <LLOQ, no descriptive statistics will be calculated for that time point. Not Applicable (NA) will be written in the field for SD and CV% and <LLOQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of <LLOQ values (n below LLOQ) will be reported for each time point along with the total number of collected values
- Three observations ≥ LLOQ are required as a minimum for a plasma concentration to be summarized. Two values are presented as a minimum and maximum with the other summary statistics as Not Calculated (NC).

For mean plots, < LLOQ values will be handled as described for the summary tabulations.

For individual plots concentrations, which are <LLOQ prior to the first quantifiable concentration, will be set to a value of zero (linear plots only). After the first quantifiable concentration, any <LLOQ concentrations will be regarded as missing. Likewise, concentrations ND and NA will be set to missing.

If concentration data at a scheduled visit is missing or its actual sampling time is out of the time window, these data will be excluded from summary table and mean plots, and these data will be flagged in subject listing and included in the individual plots.

PK parameters will be summarized and listed. Parameters following single and multiple dosing will be summarized separately. PK parameters that cannot be determined due to lack of PK concentrations will be presented as "NC" (Not calculated).

The following summary statistics will be presented for all the PK parameters (except tmax)) listed in CSP Section 3 Table 2:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Geometric standard deviation (GSD)
- Coefficient of variation (CV, calculated as 100 $\sqrt{\exp(s^2) - 1}$, where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard Deviation calculated using untransformed data
- Median
- Minimum

- Maximum
- Number of observations

The following summary statistics will be presented for t_{max}:

- Arithmetic mean
- Standard Deviation
- Median
- Minimum
- Maximum
- Number of observations

Phase 2 portion

For Phase 2 portion, plasma concentrations of acalabrutinib and acalabrutinib metabolite (ACP-5862) will be summarized and listed.

5. INTERIM ANALYSES

There is no interim analysis for futility or superiority planned for this study. There will be five planned DCOs, for details, please refer to Section 4.

6. CHANGES OF ANALYSIS FROM PROTOCOL

None.

7. REFERENCES

Cheson, B. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 3059-3067.

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Michael Hallek, Bruce D. Cheson, Daniel Catovsky, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131(25):2745-2760.

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013 Aug 8;369(6):507-516.

8. APPENDIX

8.1. CCI

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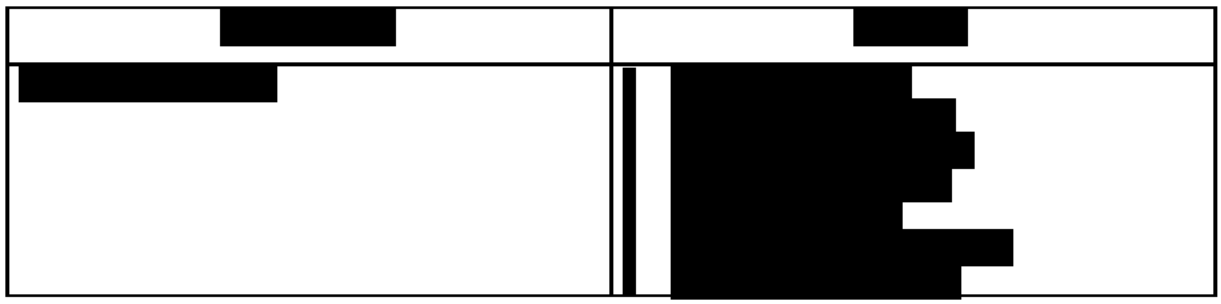

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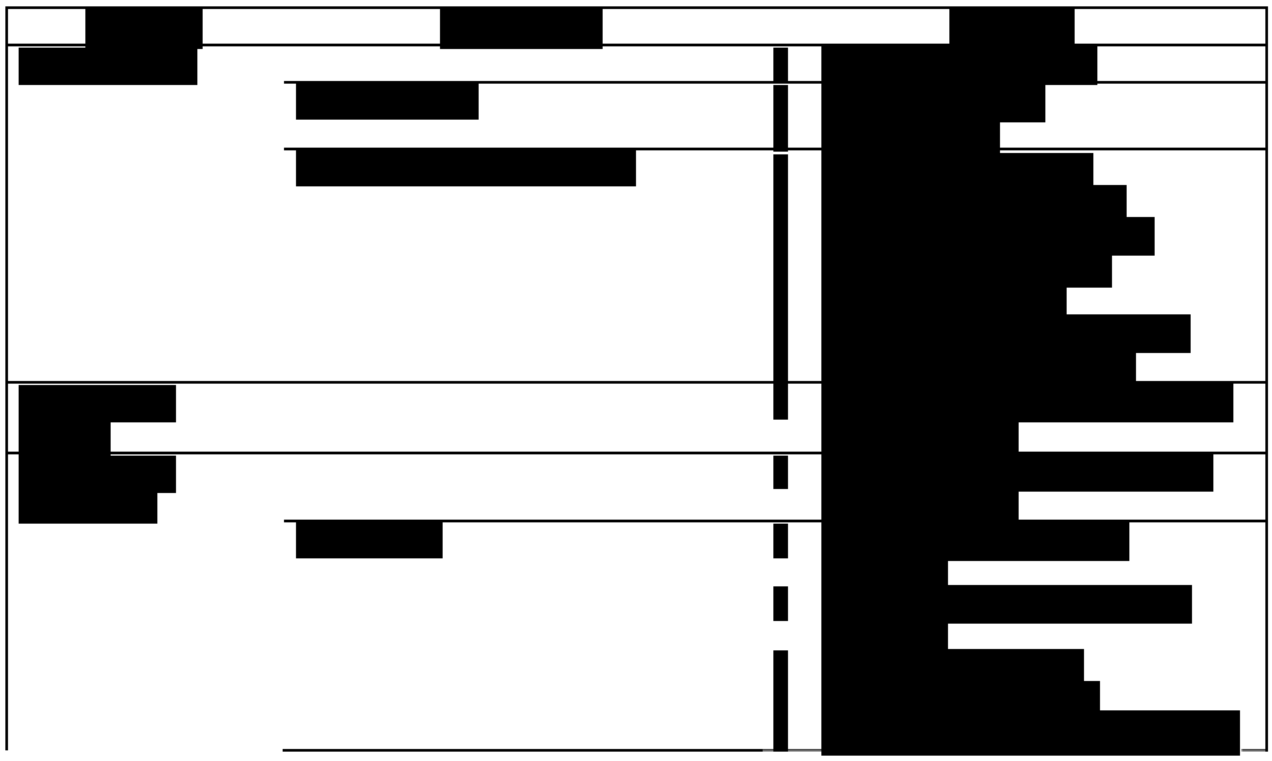


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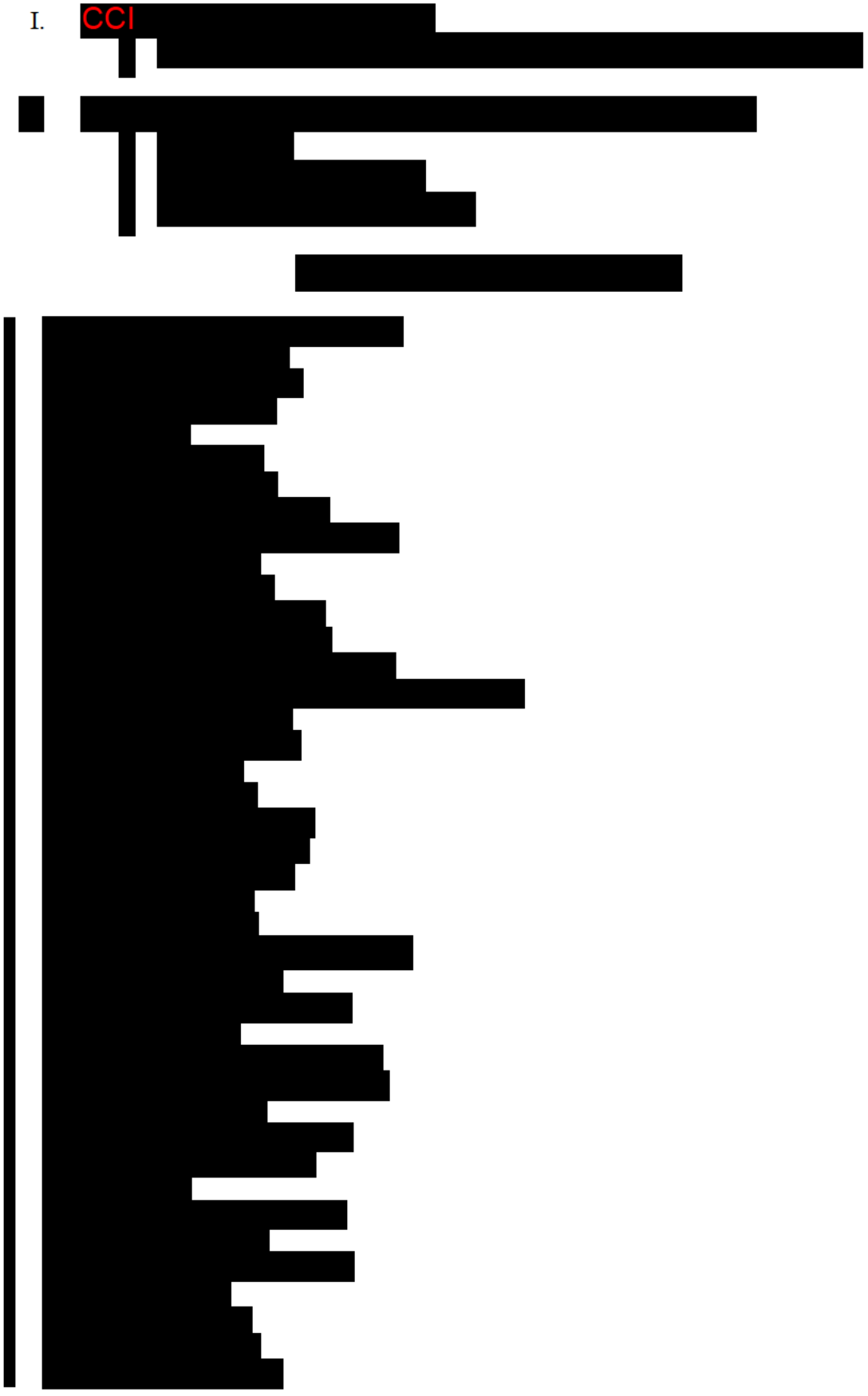
I. CCI



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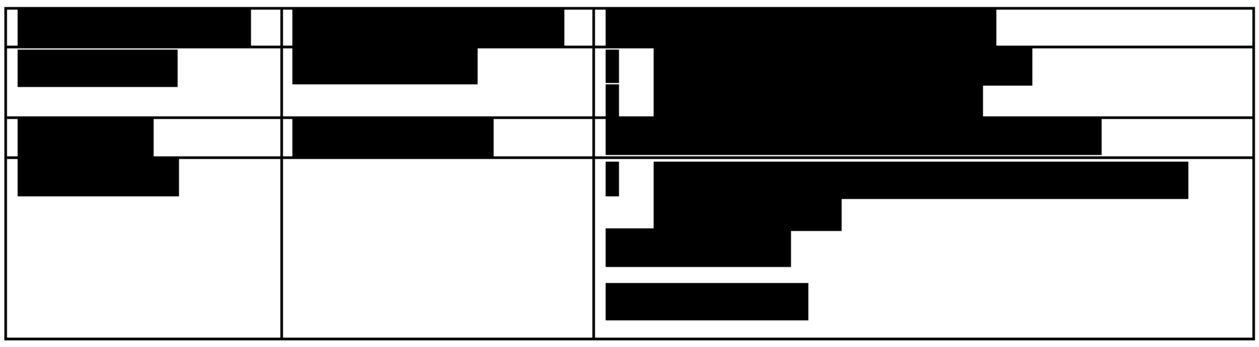

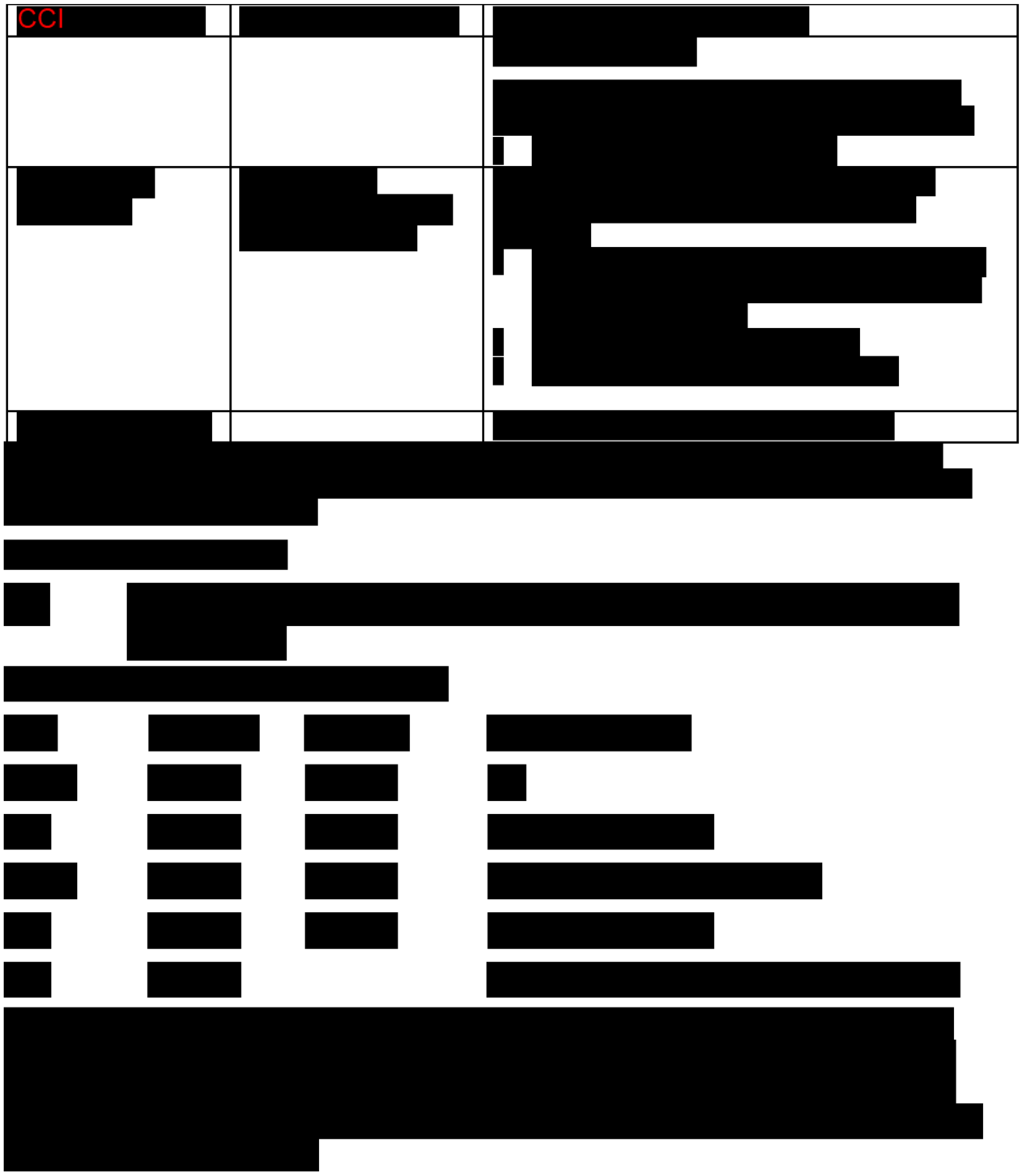
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8.4. CCI

CCI [redacted]

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