

Clinical Development

BKM120

Protocol CBKM120Z2402 / NCT01693614

**An open-label phase II study of BKM120 in patients with
relapsed and refractory diffuse large B-cell lymphoma,
mantle cell lymphoma and follicular lymphoma**

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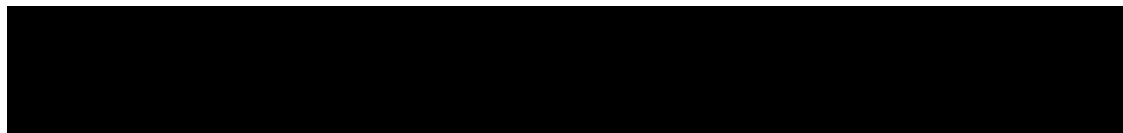
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List of abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	bis in diem/twice a day
BLRM	Bayesian Logistic Regression Model
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FAS	Full Analysis Set
FL	Follicular lymphoma
FPFV	First Patient First Visit
FPG	Fasting plasma glucose
GABA	Gamma amino-butyric acid
GI	Gastrointestinal
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human epidermal growth factor receptor 2
Hgb	hemoglobin
HIAA	Hydroxyindoleacetic acid
HIV	Human immunodeficiency virus
HSV	Herpes Simplex Virus
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRB	Institutional Review Board

IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LPFV	Last Patient First Visit
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MCL	Mantle cell lymphoma
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
NHL	Non-Hodgkin lymphomas
o.d.	<i>omnia die</i> /once a day
ORR	Overall response rate
OS	Overall Survival
p.o.	<i>Per os</i> /by mouth/orally
PD	Progressive Disease
PFS	Progression free survival
PHI	Protected Health Information
PI3K	Phosphatidylinositol-3-Kinase
PPS	Per-Protocol Set
PR	Partial Response
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
SAE	Serious Adverse Event
SEC	Safety Event Categories
SOP	Standard Operating Procedure
TBL	Total bilirubin
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
VAP	Validation Analysis Plan

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	<p>Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.</p> <p>In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.</p>
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 4 (09-Aug-2016)

Amendment rationale

The main purpose of this protocol amendment is to:

- Provide a clarification on the measures to follow when a patient exhibits suicidal ideation regardless of the response to question 9 of the PHQ-9 questionnaire (as has been described in the BKM120 Investigator's Brochure Ed. 9.0).

Rationale: Patient Health Questionnaire-9 (PHQ-9) is used to increase the sensitivity of identifying potential depression and suicidal thoughts via positive response to "question 9". However, it has not been consistently predictive for suicidal ideation or attempt in BKM120 trials, as some patients who exhibited suicidal ideation or attempt, reported as an adverse event, either had a negative response to question 9 or did not answer it. Hence, measures to be followed for any adverse event of suicidal ideation regardless of the response to question 9 or the total score of PHQ-9 have been specified in the Investigator's Brochure Ed. 9.0/dated 29-Apr-2016.

A prospective suicidality assessment in clinical trials with BKM120 is important and is facilitated using question 9 of the PHQ-9 questionnaire. A timely interview with the patient after the questionnaire completion is recommended. Patients with a positive response to question 9 (as indicated by selecting "1", "2" or "3"), or otherwise exhibiting any suicidal ideation must immediately interrupt the BKM120/placebo treatment and must be assessed by a psychiatrist. This is regardless of the response or lack of response to question 9 or total PHQ-9 score or CTCAE grading of the suicidal ideation.

Additional changes

Update to the guidelines for BKM120 administration related to food intake

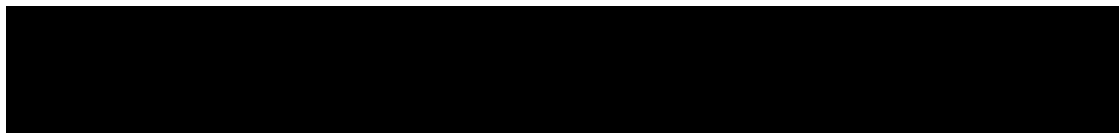
- Rationale: A clinical pharmacology study [CBKM120C2108] investigating the food effect of both a low fat low calorie meal (LFLC) or a high fat, high calorie meal (HFHC) on the pharmacokinetics of BKM120 in healthy volunteers showed that intake of food concomitantly with BKM120 led to a delayed and reduced C_{max} without a meaningful impact on exposure (AUC_{inf}) compared to fasting administration (BKM120 Investigator's Brochure Ed. 9.0). Based on these findings, BKM120 can be administered with or without food and accordingly the guidelines had been updated.

Update to the section on BKM120 dosing, without regard to food intake:

- Removal of the requirement that BKM120/placebo be taken with regard to food intake.

Changes in the section on management and follow-up for mood alteration:

- Clarification on measures to be followed (interruption of BKM120 and psychiatric consultation) for any patient who presents with suicide ideation of any grade



Changes to the study assessments:

- The inclusion of a statement that regardless of grade or response to question number 9 in PHQ-9 questionnaire, any patient who presents with suicide ideation must interrupt BKM120 and be referred for a psychiatric consultation.
- Adding a statement to require the investigator to assess the patient for suicidal ideation regardless of the answer to question 9 of PHQ-9 or if the patient did not respond to question 9 in PHQ-9 questionnaire.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The following sections have been changed in the amended protocol:

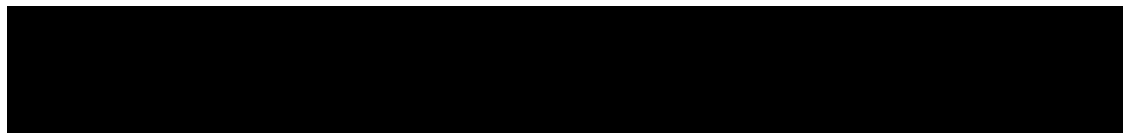
- Section 6.1.1 Dosing regimen: removal of the requirement that BKM120 be taken with regard to food intake
- Table 6-3 Criteria for interruption and re-initiation of BKM120 treatment / Mood alteration (depression, anxiety): for grade 1 and 2 the inclusion of a statement that any patient who presents with suicide ideation must be referred for a psychiatric consultation
- Section 6.3.2.1.5 Guidelines for the treatment of study drug induced psychiatric disorders. Adding a statement that any patient who presents with suicide ideation must interrupt BKM120/placebo and be referred for a psychiatric consultation regardless of grade or response to question 9 in the PHQ-9 questionnaire
- Section 7.2.2.8 GAD-7 and PHQ-9 Questionnaires:
 - Adding a statement that any patient who presents with suicide ideation must interrupt BKM120 and be referred for a psychiatric consultation regardless of grade or response to question 9 in the PHQ-9 questionnaire
 - Adding a statement requiring assessment of suicidal ideation for any patient who does not answer question 9 or the whole PHQ-9.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.



Summary of previous amendments

Amendment 3

Amendment rationale

The purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities.

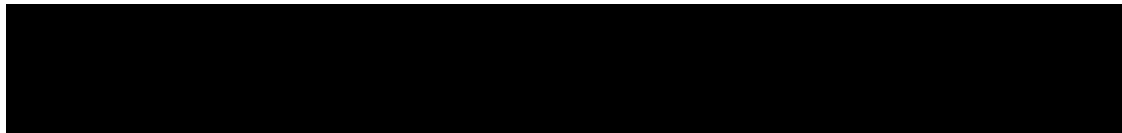
Alterations in liver function tests (LFTs) have been commonly observed in clinical trials with BKM120 as an investigational agent. These include mostly transient increases in transaminase enzymes (ALT and/or AST), which often occur during the first 6 to 8 weeks of BKM120 (buparlisib) treatment, and rarely are associated with signs/symptoms of impaired liver function. Current BKM120 protocols have conservative inclusion criteria for baseline LFTs with close monitoring guidelines to be followed during the treatment and stringent dose modification/interruption criteria.

In March 2015, a search for potential drug-induced liver injury (DILI) cases in BKM120 Novartis-sponsored trials using conservative biochemical criteria (e.g. AST/ALT $>3.0\times$ ULN and total bilirubin (TBL) $>2.0\times$ ULN at any time during the treatment period, regardless of causality) has been conducted. Upon medical review, most of these occurred in the context of disease progression in advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT $>3.0\times$ ULN and TBL $>2.0\times$ ULN in the absence of cholestasis and other explanatory causes). Five of these cases were in combination with fulvestrant in study CBKM120F2302, and one in combination with the investigational drug LDE225 (sonidegib) in study CLDE225X2114. All patients have recovered upon treatment discontinuation except one patient for whom the outcome is not available because the patient refused to return for safety follow-up. Of note, with the exception of the first case reported as Investigator notification (IN) back in April 2014, it is unknown at this stage whether the remaining patients received BKM120 or placebo as the trial remains blinded. Updated liver safety including the identified DILI/Hy's law candidates for the randomized, blinded studies CBKM120F2302 and CBKM120F2303 were further presented to the Data Monitoring Committee (DMC) in April-2015; the DMC noted no change or additional liver safety concerns and recommended continuing the respective studies as planned.

An Aggregated Safety Finding Report was submitted to Health Authorities and all investigators participating in BKM120 studies in May 2015 informing them about the liver findings including a brief summary of the six Hy's law cases. In addition, Novartis decided to update the current liver-related safety measures in ongoing protocols to enhance patient safety. Therefore, the purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities as outlined below.

Changes to the background section:

- Update of the clinical background section on liver toxicity to align with the protocol amendment rationale.



Changes to the exclusion criteria:

- Exclusion of patients with an acute viral hepatitis or with a history of chronic or active HBV or HCV infection (testing not mandatory)

Changes in the section on management and follow-up for selected toxicities:

- Addition of hepatotoxicity management guidelines

Changes to the visit schedule and assessments:

- Clarification of laboratory parameters collection plan and viral hepatitis testing.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following sections have been changed in the amended protocol:

Section 1.2.1.2 Clinical experience: addition of the outcome from a recent medical review for the liver toxicity.

Section 5.3 Exclusion criteria: Addition of exclusion Criteria #24 to exclude patients with an acute viral hepatitis or a history of chronic or active HBV or HCV infection.

Section 6.2 - Table 6-3 (Criteria for interruption and re-initiation of BKM120 treatment): Clarification of the management of AST or ALT side effects.

Section 6.3.2.2 (Additional management and follow-up for selected toxicities): New section added “Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BKM120” including detailed liver event follow-up assessments and close monitoring measures.

Section 7.1 Study flow and visit schedule - Table 7-1 (Visit evaluation schedule): addition of hepatotoxicity follow-up testing/procedures.

Section 7.1.2.3 (Patient demographics and other baseline characteristics): addition of viral hepatitis serology.

Section 7.2.2.5 (Laboratory evaluations) and Table 7-4 (Clinical laboratory parameters collection plan): addition of hepatotoxicity follow-up testing and procedures (Note: testing not mandatory).

Section 7.2.2.5.8: New section added “Viral hepatitis serology and other tests for hepatotoxicity follow-up”.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2

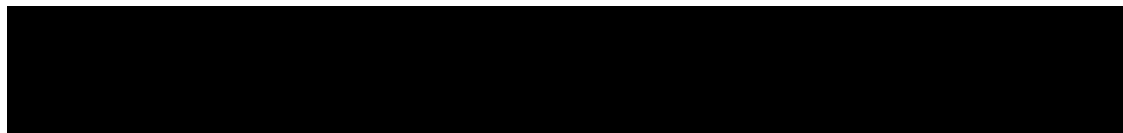
Amendment rationale

The main purpose of this protocol amendment is to update and align the management of selected adverse events across the BKM120 program and with the last [Investigator's Brochure version 6], specifically psychiatric disorders, hyperglycemia grade 2, skin rash and stomatitis (details outlined below).

In addition, a cap of N=28 patients has been added for each cohort to limit over enrollment. Despite proactive planning for cohort closure, rapid enrollment into the DLBCL cohort resulted in several additional patients in screening who then ethically had to be enrolled on trial. A similar situation might arise for MCL and FL cohorts. Hence, maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment. The method of statistical analysis remains the same, knowing that the power and rejection rule may change with the final number of patients enrolled as described in Table 10-1.

Modification in the BKM120 interruption period to recover from an adverse event is extended from 21 to 28 days before the patient has to be permanently discontinued from study treatment. The maximum allowed treatment interruption for BKM120 after which the treatment has to be permanently discontinued will be increased from 21 to 28 days since the recovery to \leq grade 1 has been reported to take longer for some of the side effects (e.g. skin rash, transaminase increase). This will allow sufficient time for recovery, implementation of appropriate clinical management and/or external consultation (e.g. involvement of a psychiatrist for psychiatric disorders, etc.) should this be needed. Grade 4 AEs will still continue to lead to permanent discontinuation for most AEs (irrespective of recovery time). Patients who experience treatment interruptions because of an adverse event will further resume treatment with a reduced dose after recovery in most cases (see specific tables for dose adjustment guidelines). In addition, the investigator may decide to discontinue the patient at any time if this is in the best interest of the patient.

Moreover, to improve clarity, changes have been implemented to the inclusion/exclusion criteria, definition of post-menopausal status, collection of outcomes from pregnant partners of male study participants, as well as editorial changes.



Changes to the inclusion/exclusion criteria:

- Clarification that inclusion of patients with total bilirubin values below the lower limit of normal is allowed as such values are considered not clinically relevant for the purpose of entry into the study [inclusion criterion #8].
- Patients with active severe personality disorders will be excluded to align with changes within the program based on clinical experience from ongoing BKM trials as reflected in the updated information in the current IB version 6.0 issued on 13-Nov-2013, and with additional feedback from earlier advisory boards [exclusion criterion #8].
- Postmenopausal status definition has been clarified and aligned with the NCCN guidelines [National Comprehensive Cancer Network 2012- www.nccn.com]. Postmenopausal range for hormone levels is either serum FSH >40 mIU/mL and estradiol <20 pg/mL, or according to the respective postmenopausal range definition used by the laboratory involved [exclusion criterion #26].

Changes to the management of psychiatric disorders, hyperglycemia grade 2, skin rash and stomatitis:

- To align with changes within the program based on clinical experience from ongoing BKM trials as reflected in the updated information in the current IB version 6.0 issued on 13-Nov-2013, and with additional feedback from earlier advisory boards, the following changes are implemented to simplify the evaluation of psychiatric disorders. Psychiatric disorders must be based on clinical assessment only, according to NCI-CTC 4.03; independently from patient self-reported mood questionnaires.
 - Patients with active severe personality disorders will now be excluded, and Section 6.3.2 has been revised to clarify the dose modification and interruption for mood alterations. In addition, specific guidelines for the treatment of study drug induced psychiatric disorders has been added (Section 6.3.2.1.5).
 - Section 7.2.2.8 is revised to clarify that the grading of psychiatric disorders must be based on clinical assessment only, according to NCI-CTC 4.03, independently from patient self-reported mood questionnaires.
 - Section 7.2.2.8 is revised to clarify that patients who answer positively to question 9 of PHQ-9 (suicidal risk) must omit treatment with BKM120 and must be referred for psychiatric consultation to mitigate potential suicide risk. Psychiatric consultation will confirm if study drug should be interrupted or permanently discontinued. Moreover, psychiatric consultation is further required for patients who develop CTC AE grade 3 or 4 psychiatric disorders
- Hyperglycemia is a common side effect of BKM120 treatment. However, there is no immediate or subacute safety risk for patients experiencing grade 2 hyperglycemia. Therefore, the management guideline for grade 2 hyperglycemia has been amended and closer aligned with the recently published NCI task force guidelines on hyperglycemia and metabolic disorders associated with mTOR/PI3K inhibitors ([Busaidy et al 2012](#)). This will better allow installing appropriate anti-glycemic therapy. No changes are made for symptomatic, or grade 3 or 4 hyperglycemia, which are still managed conservatively.

- Skin rash is a common side effect associated with BKM120 treatment which can be severe and potentially lead to treatment interruption or discontinuation. Thus, more conservative dose interruption/modification guidelines are instituted for grade 2 and 3 skin rash.
- Stomatitis is occurring in up to 25% of patients receiving BKM120 monotherapy [Investigator Brochure version 6]. Guidelines are added to support investigators in the management of this adverse event.

Update to prohibited concomitant medications:

- Wording added in the prohibited concomitant therapy section to clarify the wash-out period for prohibited concomitant therapies (e.g. prohibited concomitant therapy should be stopped at least 5 half-lives or 7 days before start of study treatment (Cycle 1 Day 1).

As of December 11, 2013, 52 patients have been enrolled in the study CBKM120Z2402.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Protocol Summary Exclusion criteria: mTOR inhibitors was removed from the first exclusion criterion listed. This should have been removed in Amendment 1 when the change was made.

Protocol Summary Efficacy Assessments: “Objective response rate” updated to “Overall response rate”. Overall response rate is the proportion of patients with best overall response of CR or PR. This is also referred to as “Objective response rate”. All instances of “objective response rate” have been updated to “overall response rate” for consistency.

Protocol Summary Data analysis: updated to clarify that maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment.

Table 3-1: Updated to include definitions of endpoints as per protocol.

Figure 4-1: Note added that maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment.

Section 5.2: Inclusion # 8 was updated to clarify that calcium levels should be corrected for albumin. The lower normal limit constraint for total bilirubin was removed and further clarification was provided regarding Gilbert Syndrome.

Section 5.2: Exclusion criteria #8: Addition to specify that patients with active severe personality disorders (defined according to DSM-IV) are not eligible.

Section 5.2: Exclusion criteria #20: Additional examples, including immunocompromised, chronic pulmonary disease including dyspnea at rest or interstitial lung disease, uncontrolled hypertension, have been added for clarification.

Section 5.2 Exclusion criteria #26: Clarification on the definition of postmenopausal status to align with NCCN guidelines.

Section 6.1.1.1: To limit the potential impact of H2 antagonists, in this study BKM120 will be administered at least one hour before or 10 hours after H2 antagonists (or proton pump inhibitor, antacid, etc.) administration.

Section 6.3.2: Clarifications provided related to additional exams in Table 6-3. Updated number of days permitted for study treatment interruption.

Section 6.3.2.1: Criteria for BKM120 dose modification and Table 6-2 modification

Section 6.3.2.1: Table 6-3: Criteria for interruption and re-initiation of BKM120 treatment. Modification for FPG, Mood alteration, Fatigue, Rash and addition of criteria for Stomatitis/Oral mucositis.

Section 6.3.2.1.3: Guidelines for the treatment of study drug induced stomatitis/oral mucositis:

Addition of Section 6.3.2.1.5: Guidelines for the treatment of study drug induced psychiatric disorders.

Addition of Section 6.3.2.1.6: Minor changes in wording on guidelines for the treatment of study drug induced skin toxicity.

Section 6.4.2: Clarified that prohibited concomitant therapy should be stopped at least 5 half-lives or 7 days before cycle 1 day 1 and must not be used while the patient is on study.

Section 6.4.2.6, Table 14-3 and Table 14-4 updated to include website (<http://crediblemeds.org/>) for a comprehensive list of agents that prolong the QT interval

Section 7.1.5.1: Updated number of days permitted for study treatment interruption.

Section 7.2.1.2: Updated maximum number of days from tumor assessment to first dose of study drug to be consistent with Visit Schedule. Changed from 21 days to 28 days.

Section 7.2.2.5.7: Updated the definition of postmenopausal status to align with NCCN guidelines.

Section 7.2.2.8: Description of mood alteration questionnaires and their administration.

Management of mood alterations: Toxicity grading table was deleted to add the severity classification table instead. Specification that for patients who indicate a positive response by selecting “1, 2, or 3” to the question number 9 in the PHQ-9 questionnaire must stop treatment with BKM120 and must be referred for psychiatric consultation. Clarification of severity based on mood questionnaire score Table 7-5 updated.

Section 8.1.1: Updated Death form to EOT/SEC/Survival Information eCRF pages.

Section 8.4: Included guidelines for the collection of pregnancy outcomes for the female partners of any males who took study drug in this study.

Section 10: Updated to clarify that the maximum number of patients per cohort will capped at N = 28 patients, in case of over enrollment and removed pharmacokinetic measurements.

Section 10.5.2: Updated to clarify that duration of response is defined as the time from the date of first occurrence of CR or PR to the date of the first documented progressive disease (PD) or death due to lymphoma per Cheson criteria.

Section 10.5.3.4: Updated to include safety analysis of mood questionnaires.

Section 10.8: Updated to include the over enrollment scenario. In addition, a cap of N=28 patients has been added for each cohort to account for over enrollment. Due to the rapid enrollment into the DLBCL cohort and despite early planning for cohort closure, the study team encountered too many additional patients already in screening who could not be declined enrollment due to ethical reason. Also similar situation might arise for MCL and FL cohorts. Hence, maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment. The method of statistical analysis remains the same, knowing that the power and rejection rule may change with the final number of patients enrolled as described in Table 10-1.

Table 14-1: Reference was mentioned twice. Typo was corrected.

Table 14-2: First asterisk in footer was removed since it did not correspond to anything within the table.

Section 14.5.1: Updated to clarify that Appendix 5 consists of general guidelines some of which have been modified for this protocol:

- Only patients with measurable disease at baseline are being considered for this study
- Randomization is not applicable to the study since it is a non-randomized trial. All responses will be calculated from start of treatment.
- If a lesion splits during the study, the sub-lesions will not be measured separately. Instead, such lesions which have split into sub-lesions will be measured as one lesion with all sub-lesions contributing to the overall SPD.
- Central Blinded Review of radiological response will not be used for this study. Responses will be assessed by the Investigator.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

The primary purpose for amending the protocol is to include monitoring for evidence of tumor lysis syndrome during treatment with BKM120. Tumor lysis syndrome (TLS) may occur during treatment for diffuse large B-cell lymphoma; therefore the protocol and visit schedule

are being amended to include appropriate monitoring for evidence of TLS during the first 72 hours of study treatment.

In addition, the requirement for not allowing previous treatment with mTOR inhibitors has been removed from the exclusion criteria. Temsirolimus, an mTOR inhibitor, is approved in some countries for mantle cell NHL. Since BKM targets PI3K and not mTOR, there is no reason to exclude these patients. Removing this exclusion would also broaden eligibility for this population that has significant unmet medical need and potentially no anticipated impact on study results.

This amendment also includes a correction to the exclusion criterion regarding types of effective contraception which can be used throughout the study. Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving BKM120. Hormonal contraception must not be used during BKM treatment and has been removed from the list of acceptable contraceptives.

Several other exclusion criteria have been modified to provide further information or clarification. One additional exclusion criterion has been added to exclude patients who are currently receiving warfarin or other coumarin derived anti-coagulant for prophylaxis.

In addition, this amendment includes other administrative corrections and clarifications.

The study has not yet opened and is not currently enrolling patients.

Changes to the protocol

Section 4.1: End of treatment visit will occur within 7 days following discontinuation of BKM120.

Section 5.2: The upper limit of normal (ULN) associated with International Normalized Ratio (INR) has been removed from inclusion criterion #8 as no ULN is specified for INR.

Section 5.3

- Previous treatment with mTOR inhibitors has been removed from exclusion criterion #1. Patients who have had previous treatment with mTOR inhibitors may be enrolled.
- Exclusion criterion #19 has been clarified to exclude patients receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (> 5 days) can induce CYP3A4.
- Exclusion criterion #21 has been updated to exclude patients unable to grant consent.

- Exclusion criterion #22 has been updated to include clarification as to when strong CYP3A4 inducers and inhibitors must be discontinued prior to start of treatment has. Patients must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment
- An additional exclusion criterion (#23) has been added to exclude patients who are currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
- The use of hormonal contraception has been removed from the list of acceptable forms of effective contraception provided in exclusion criterion #26. Hormonal contraception must not be used during BKM treatment as stated in Section 6.4.2.9. The criterion has also been updated to clarify that female partners of male study subjects should use contraception through 16 weeks after final dose of male subject.
- Exclusion criterion #27 has been clarified to exclude patients with a known hypersensitivity to any of the excipients of BKM120.

Section 6.4: Paclitaxel has been removed as the study involves only one treatment (BKM120).

Section 6.4.1.5 (Bisphosphonates) has been removed since these are not part of the standard management of NHL patients.

Section 6.4.1.7: Allopurinol or rasburicase have been added as permitted concomitant therapy. Allopurinol and rasburicase may be used at the physician's discretion in DLBCL patients at risk for tumor lysis syndrome.

Section 6.5.1 has been updated to include additional information about re-screening patients. Re-screening is permitted for patients as long as all screening procedures are performed within the specific time window. Any re-screened patient must retain the same Subject No. Re-screening of patients is only allowed once per patient.

Section 7.1: Safety follow-up visit window has been updated to +7 days.

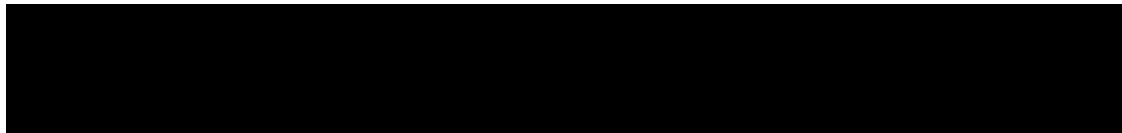
Section 7.1.5: The window for the end of treatment visit has been updated. The end of treatment visit and evaluations must occur within 7 days from treatment discontinuation.

Table 7-1 and Section 7.2.2.5.2: The visit evaluation schedule (Table 7-1) and section have been revised to include assessments for TLS during the initial 72 hours of study treatment in patients with diffuse large B-cell lymphoma. Blood tests for uric acid, potassium, sodium, calcium, inorganic phosphorus and serum creatinine will be assessed on days 2, 3 and 4 of the first cycle in DLBCL patients only.

Section 7.2.2.5.2 has also been updated to include further details regarding the frequency of laboratory evaluations.

Section 7.2.2.5.7 has been updated to clarify that only serum pregnancy testing will be performed throughout the study. Urine pregnancy testing is not permitted.

Section 7.2.2.8 has been made consistent with the visit evaluation schedule. The mood questionnaires (PHQ-9 and GAD-7) must be completed at all study visits. This section has also been updated with additional details and clarifications regarding the questionnaires.



Section 8.7 has been updated to include a Steering Committee.

Section 14.5 Appendix 5 has been updated to remove comments and notes.

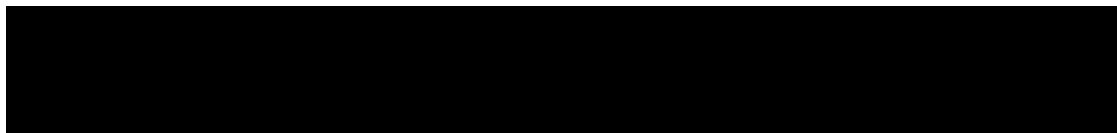
Additional minor editorial corrections have been made throughout the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.



Protocol summary:

Protocol number	CBKM120Z2402
Title	An open-label phase II study of BKM120 in patients with relapsed and refractory diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma
Brief title	Study of BKM120 in relapsed and refractory NHL
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>The purpose of this study is to explore therapeutic efficacy of BKM120 in three selected types of NHL, including DLBCL, MCL and FL, and the safety/tolerability of patients.</p> <p>Inhibitors of the PI3K/mTOR/Akt pathway, including BKM120, may be therapeutically effective in NHL patients based on the observations from both pre-clinical and early phase clinical trials with either selective or non-selective inhibitors of the PI3K/mTOR/Akt pathway. As pan class I PI3K inhibitors demonstrate evidence of efficacy in solid tumor patients and since there are several p110 isoforms detected in B cell NHLs, this presents an intriguing opportunity for further evaluation of BKM120.</p>
Primary Objective(s) and Key Secondary Objective	To determine the efficacy of BKM120 in patients with relapsed/refractory Non-Hodgkin Lymphoma in the three different histological subgroups
Secondary Objectives	<p>To evaluate the safety and tolerability in the three different histological subgroups</p> <p>To assess progression free survival in the three different histological subgroups</p> <p>To assess the duration of response in the three different histological subgroups</p> <p>To assess overall survival in the three different histological subgroups</p>
Study design	This is an open label phase II study in patients with relapsed and refractory Non-Hodgkin Lymphoma including 3 histological subgroups (cohorts): diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL). The primary efficacy and safety analysis for each cohort will be performed when all patients included in the corresponding cohort experienced progression, discontinued early or 6 months after the last patient has started the first cycle of treatment. An update of the analyses will be conducted after all enrolled patients have completed the study.
Population	Patients with histologically confirmed relapsed or refractory diffuse large B cell lymphoma, mantle cell lymphoma and follicular lymphoma.

Inclusion criteria	<ol style="list-style-type: none"> 1. Patient has a histologically confirmed diagnosis of mantle cell lymphoma, follicular lymphoma, or diffuse large B cell lymphoma. 2. Patient has relapsed or refractory disease and received at least one prior therapy 3. Patient with diffuse large B cell lymphoma has received or is ineligible for autologous or allogeneic stem cell transplant. This does not apply to patients with mantle cell lymphoma and follicular lymphoma. 4. Patient has at least one measurable nodal lesion (≥ 2 cm) according to Cheson criteria (Cheson et al 2007). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at baseline, then the patient must have at least one measurable extra-nodal lesion. 5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 6. Patient has adequate bone marrow and organ function
Exclusion criteria	<ol style="list-style-type: none"> 1. Patient has received previous treatment with PI3K inhibitors 2. Patient has evidence of graft versus host disease (GVHD) 3. Patient has active or history of central nervous system (CNS) disease 4. Patient has a concurrent malignancy or has a malignancy within 3 years of study enrollment (with the exception of adequately treated basal or squamous cell carcinoma or non-melanomatous skin cancer) 5. Patient has a score ≥ 12 on the PHQ-9 questionnaire. 6. Patient has a GAD-7 mood scale score ≥ 15. 7. Patients with an acute viral hepatitis or a history of chronic or active HBV or HCV infection
Investigational and reference therapy	BKM120
Efficacy assessments	<ul style="list-style-type: none"> - Overall Response rate (ORR) - Progression Free Survival (PFS) - Duration of Response - Overall Survival (OS)
Safety assessments	- Frequency and severity of adverse events; other safety data as considered appropriate
Other assessments	
Data analysis	The primary endpoint of the study is Overall Response Rate (ORR) defined the proportion of patients with a best overall response of CR or PR according to Cheson criteria (Cheson et al 2007). The analysis for each cohort will be based on an exact binomial test comparing the ORR to the reference level of 10%. The test for each cohort will use a significance level of 5%. A significant test result is achieved when at least 6 responses are observed among the 22 patients in each cohort. Maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment. The ORR will be presented together with an exact 95% Clopper-Pearson confidence interval.
Key words	PI3K inhibitor, BKM120, Non-Hodgkin lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

The Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment ([Armitage 1993](#)). Like Hodgkin lymphoma, NHL usually originates in lymphoid tissues and can spread to other organs. NHL, however, is much less predictable than Hodgkin lymphoma and has a far greater predilection to disseminate to extranodal sites.

NHL represents 4% of all types of cancer. The risk of NHL during a person's life time is one in 50 people (about 2%). Men have slightly higher chances than women to have NHL ([American Cancer Society 2012](#)). There are estimated 70,130 new cases of NHL and about 18,940 deaths in the United States in 2012 ([National Cancer Institute 2012](#)). NHL can occur at any age and is often marked by lymph nodes that are larger than normal, fever, and weight loss. NHL is now the 5th leading cause of cancer in both men and women. NHL is a disease of aging; for unclear reasons, the incidence of NHL continues to increase. With the increasing age of the population, NHL is an important cause of morbidity and mortality in adults.

NHL can be divided into aggressive (fast-growing) and indolent (slow-growing) types, and can arise from either B-cells or T-cells. B-cell NHL represents 85% of all NHL, and include Burkitt lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma (MCL).

Though considered a curable disease, about 50% of NHL patients are not cured with available therapy, and this remains an important cause of morbidity and mortality in adults. Novel therapies with unique mechanisms of action unaffected by common drug resistance mechanisms must be developed to improve treatment outcomes. The current 5-year and 10-year survival rates for lymphoma are 63-67% and 51-55%, respectively ([American Cancer Society 2012](#)).

The diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma are among of those most commonly seen NHLs, and are the malignancies targeted in this study.

1.1.1 Overview of diffuse large B cell lymphoma

DLBCL comprises more than 30% of all newly diagnosed NHL cases. Majority (over 80%) are aggressive lymphomas, and more than half of these patients are older than 60 years. The outcome for patients with DLBCL has significantly improved over the last decade and around 50% of DLBCL patients can be cured with rituximab and chemotherapy. The other 50% of DLBCL patients, especially the poor risk patients (International Prognostic Index of 3, 4 or 5 factors), will relapse or progress despite a good initial response to the front line immuno-chemotherapy. High-dose chemotherapy with autologous stem-cell transplantation (ASCT) is an established treatment option for poor-prognosis patients who are 65 or younger and refractory to front line therapy. Nevertheless, more than half of these patients will relapse

following ASCT/high dose chemotherapy and die of the disease. The prognosis among patients who are not transplant candidates is even more dismal.

Novel drug therapy with different mechanisms to prolong duration of disease remission in poor risk patients and eventually to improve long term survival among these patients is a pressing need.

Single agent everolimus (AFINITOR[®], RAD001), an inhibitor of the mammalian target of rapamycin (mTOR) has demonstrated substantial anti-tumor activity in relapsed aggressive NHL and other types of relapsed or refractory lymphomas, including MCL, indolent and other uncommon lymphomas.

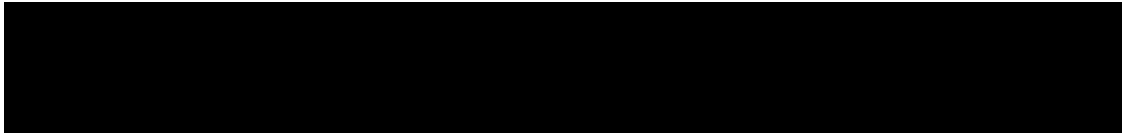
1.1.2 Overview of mantle cell lymphoma

MCL has been classified as a subgroup of aggressive diffuse low grade B cell lymphomas. MCL is a unique subtype of NHL characteristic with the t(11;14) (q13;q32) balanced chromosomal translocation of the *cyclin D1* gene (*bcl-1*) on chromosome 11 to the immunoglobulin heavy chain (IGH) enhancer region on chromosome 14, which results in Cyclin D1 over expression and increased cell proliferation of the tumor cells (Witzig et al 2005). With a prevalence of 5% to 6% of all NHL, MCL accounts for up to 8000 newly diagnosed NHL cases in US and EU each year.

With the exception of rare patients who enjoy long term disease-free survival after non-myeloablative allogeneic stem cell transplantation, patients with MCL have the worst prognosis of all NHL subtypes. Most MCL patients are treated with rituximab (Rituxan[®]/Mabthera[®]), directed against CD20 (a B lymphocyte specific antigen), in combination with different chemotherapy regimens. The initial treatment usually yields a high response rate, however, most patients relapse following initial therapy and their median survival is about 1-2 years (Fisher et al 2006). As there is no standard therapy for newly diagnosed or relapsed patients with MCL and the treatment remains suboptimal, new agents are beginning to emerge.

Bortezomib (Velcade[®]) is an intravenous proteasome inhibitor that was approved in the US in 2006 for treatment of MCL in patients with a history of one prior treatment. The response rate to Velcade[®] therapy was 33%, including 8% complete responses. The median time to progression (TTP) was 6.2 months. With an average follow-up of 13.4 months, the median overall survival (OS) was not reached (Fisher et al 2006). Velcade[®] has not been approved for treatment of MCL in the EU, however it is approved by the European health authorities for treatment of patients with multiple myeloma.

Data on the efficacy and safety of temsirolimus (Torisel[®], CCI-779), an intravenous mTOR inhibitor, as a single agent in patients with relapsed or refractory MCL have been published by (Witzig et al 2005). Thirty-five patients were treated in this study with temsirolimus 250 mg intravenously every week as a single agent. Patients had previously received a median of 3 prior therapies and 54% had been refractory to the last therapy. The overall response rate was 38% (95% CI: 22% to 56%), with one complete response and 12 partial responses. Median time to progression was 6.5 months (95% CI: 2.9 to 8.3 months). The authors concluded that single-agent temsirolimus has substantial antitumor activity in relapsed MCL. A similar



response rate of 29% (4 out of 14) has been observed in a phase II trial of 10 mg daily everolimus in patients with MCL ([Reeder & Gornet ASH 2007](#)). In a multicenter phase II trial of single-agent everolimus in patients with relapsed or refractory mantle cell lymphoma, complete response (CR) was achieved in two patients and partial response (PR) in five patients, resulting in an objective response of 20% (95% CI 8-37%) and an additional 17 patients (49%) achieved disease stabilization (SD) ([Renner et al 2012](#)). A large international trial (PILLAR-1) with everolimus in relapsed/refractory MCL has completed enrollment and data are awaited.

1.1.3 Overview of follicular lymphoma

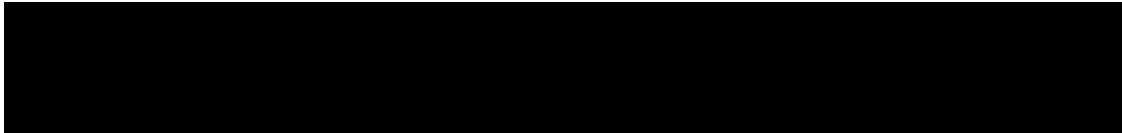
FL is the second most common form of NHL prevailing in the United States. Despite an advanced stage, the clinical course of disease is usually indolent and patients are highly responsive to various combinations of standard chemotherapy drugs. The disease, however, is not curable with available treatment, and most patients tend to relapse after treatment with shorter intervals of remission in between. In approximately 30% of patients, the disease progresses more rapidly with transformation into DLBCL and early death. The molecular biology underlying this phenomenon and the factors associated with the risk of transformation are not entirely known.

The incorporation of effective and well-tolerated monoclonal antibodies, such as rituximab, into chemo-immunotherapeutic strategies provided the first evidence that survival of these patients could be prolonged. A relatively small pivotal phase II study in 166 patients with relapsed FL resulted in rituximab being the first FDA approved monoclonal antibody for the treatment of cancer. The combination of rituximab and chemotherapy (R-Chemo) has resulted in greatly improved response rates, progression free survival and also overall survival, to such an extent that R-Chemo is now worldwide the standard induction treatment in first line as well as for relapsed advanced stage FL.

Nevertheless, FL remains incurable and characterized by recurrent relapses requiring additional treatment. An increasing number of effective drugs are now being evaluated either alone or in combinations including the chemotherapy drugs bendamustine and bortezomib. More targeted agents include monoclonal antibodies and their derivatives such as drug-antibody conjugates and small modular immunopharmaceuticals. Other agents inhibit various cellular pathways including those triggered by the B-cell receptor, including spleen tyrosine kinase (Syk) and Bruton's tyrosine kinase, and other intracellular pathways such as the mTOR, Phosphatidylinositol-3-Kinase (PI3K), and apoptosis, and drugs that target the tumor microenvironment. This abundance stresses the unrelenting need for clinical trials aimed at answering the many open questions as to optimal treatment strategies in advanced FL ([Cheson 2011](#)).

1.1.4 The PI3K pathway

The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis ([Katso et al 2001](#)). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. At the structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. The



PI3K signaling is modulated by multiple regulators, including growth factors (such as EGF, IGF-1, and FGF), hormones (such as estrogen and thyroid hormone), integrins, intracellular calcium levels, and RAS signaling. PI3K signaling is negatively regulated at the level of PIP3 clearance by phospholipid phosphatases, such as the phosphatase and tensin homologue (PTEN) protein and the inositol 5-phosphatase-2 (SHIP2) protein.

Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types ([Liu et al 2009](#)). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway ([McCubrey et al 2006](#)). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.

Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to,

- a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110 α ; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or
- b. Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of PTEN expression or function) ([Chow & Baker 2006](#), [Cully et al 2006](#))

Together these observations suggest that PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced solid malignancies who often have limited therapeutic options beyond institutional standard of care. Hence, the pan-PI3K inhibitor BKM120 treatment potentially addresses an unmet medical need in such patients

A schematic representation of these PI3K components is shown in [Figure 1-1](#).

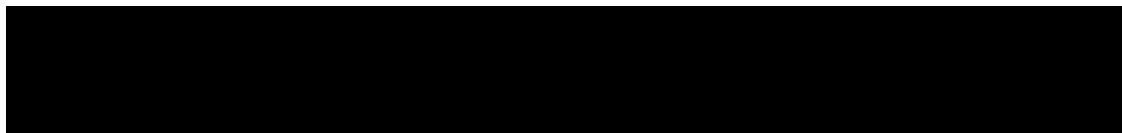
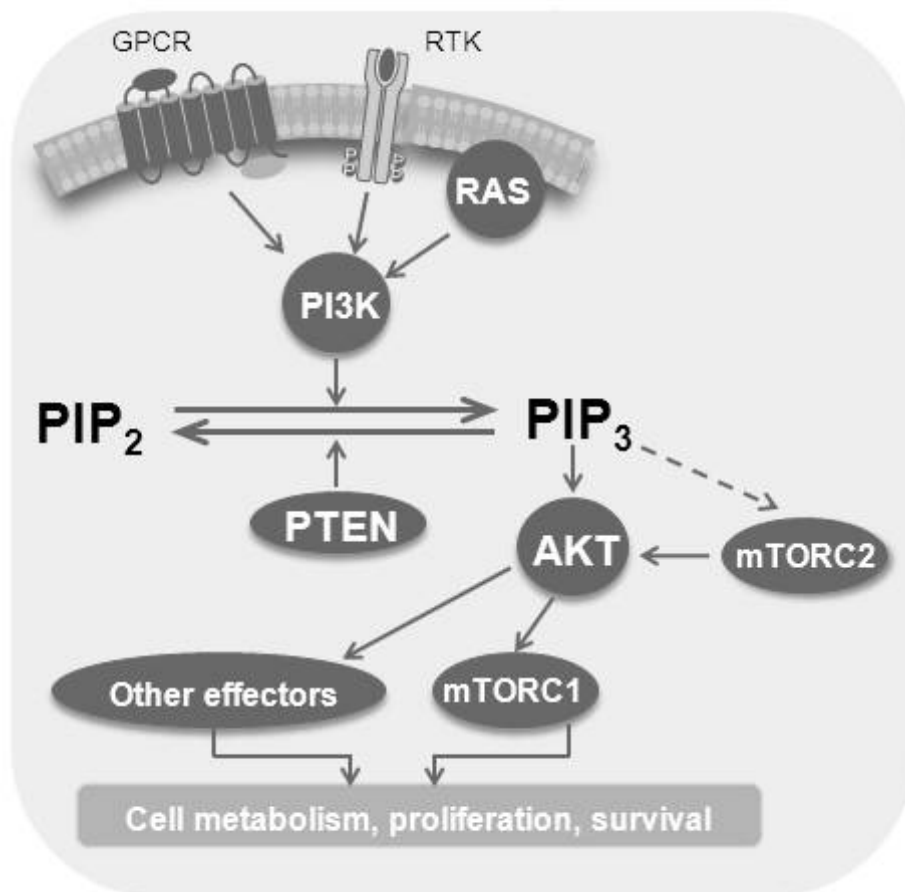


Figure 1-1 Schematic representation of the PI3K pathway



1.1.5 The PI3K/mTOR/Akt pathway and NHL

Pre-clinical and early-phase clinical studies support the rationale of inhibiting the PI3K pathway for NHL.

1.1.5.1 Observations from pre-clinical studies

The PI3K pathway is an intracellular component of the B-cell receptor signaling pathway that regulates the cell cycle and is implicated in the development of many malignancies, including lymphoma, leukemia, and many solid tumor malignancies. Unregulated activation of Akt has been demonstrated in MCL, both in cell lines and in patient samples. Also, PI3K inhibition decreased expression of NF- κ B and CyclinD1, and induced apoptosis (Rudelius et al 2006). Additionally, overexpression of phosphorylated Akt by immunohistochemistry was observed in tissue samples from patients with MCL. There was decreased expression of downstream targets of Akt and increased apoptosis when these cells were exposed to a PI3K inhibitor (Dal Col et al 2008). Akt upregulation is also demonstrated in tissue samples of follicular lymphoma (FL) (Zha et al 2004), while expression of pAKT was observed in 52-72% primary DLBCL samples, indicating activation of the pathway in these histological subtypes of NHL. Reduction, or loss of PTEN expression was also reported in 76/215 (37%) primary DLBCL samples (Baohua et al 2008, Abubaker et al 2007, Uddin et al 2006).

Preclinical data suggests that targeting any of the PI3K/Akt/mTOR components can induce tumor cell death in a variety of lymphoid malignancies. BKM120, the investigational compound in this study, is a pan class I oral PI3K inhibitor, including the p110 α , β , γ , and δ isoforms. It has demonstrated its activity in lymphoma cell lines, including mantle cell lymphoma, where it resulted in at least a 2-fold down-regulation of the myc-dependent proliferation, measured by gene expression (Walsh et al 2009).

The pan-PI3K inhibitor, SF1126 exhibited >90% decrease in pAkt and pGSK-3 β . SF1126 induced apoptosis in a dose and time dependent manner confirmed by flow cytometry. SF1126 induced G1 cell cycle to suppression of cell proliferation. The cell cycle protein cyclin D1, a hallmark of MCL was significantly decreased by SF1126 demonstrating that SF1126 potently inhibits the constitutively activated PI3K/mTORC/Akt pathway in aggressive B-cell NHL cell lines with consequent suppressive effects on cell cycle progression, cell proliferation and induction of apoptosis in aggressive B-cell NHL (Mahadvan et al 2011).

CAL-101, a selective inhibitor of the p110 δ isoform of PI3K, has shown activity in vitro against B-cell malignancies. Treatment of cell lines from CLL and MCL also demonstrated significant reduction in Akt, indicative of inhibition of the pathway. In addition, in FL cell lines demonstrating increased pAkt at baseline, there was a concentration-dependent reduction in pAkt and the downstream target pS6 when treated with CAL-101 (Lannutti et al 2011). CAL-101 could disrupt signals from the microenvironment, induce apoptosis, and enhance the antitumor activity of everolimus in MCL. The pAkt decrease was associated with growth suppression and induction of apoptosis in all MCL cell lines. CAL-101 decreased cyclin D1 levels in MCL cell lines (Meadows et al 2011).

While the p110 δ isoform of PI3K is found in B cells, it could become a suitable target for a selective PI3K inhibitor (i.e. CAL-101). As additional isoforms such as p110 α and p110 β are also found in B cells, given their association with the B cell receptor signaling pathway, these isoforms would potentially be additional targets for B-cell lymphoma therapy. In fact, treatment of MCL cell lines with a selective inhibitor of p110 α as well as with a non-selective PI3K inhibitor induced tumor cell growth inhibition, while a selective inhibitor of p110 δ did not (Zhou et al 2010).

1.1.5.2 Observations from early phase clinical trials

CAL-101 was also tested in early phase clinical trials in patients with NHL. In a Phase I study, CAL-101 was evaluated for its safety and clinical activity in patients with select hematologic malignancies including relapsed/refractory CLL or select B-cell NHL. Approximately 12 patients each with CLL, indolent NHL, aggressive NHL, and AML were to be enrolled. CAL-101 was administered orally twice daily continuously for 28 days per cycle. Clinical response was evaluated at the end of Cycles 1 and 2 and every 2 cycles thereafter. To date, 43 patients have been enrolled and followed for at least 4 weeks, consisting of 17 patients with CLL 9 patients with indolent NHL, 10 patients with aggressive NHL and 7 patients with AML. The demographic and disease characteristics were 33% female, mean age 65 (60% over age 65), 49% had refractory disease and the median number of prior regimens was 5. The median duration of treatment at data cutoff was 3 cycles (range 1 to 10). Two patients discontinued early due to adverse events, one for acute on chronic renal failure and one for abnormal liver

function tests (LFTs). DLTs were observed in 5 patients with increases in LFTs, which resolved following discontinuation of CAL-101 dosing. No patient had grade 4 hematological toxicity. Serious infections were reported in 9 patients, with pneumonia being the most frequent. 41 patients were evaluable for clinical response. At data cutoff, the response rate in NHL was 10/18 (56%); all were partial responses (PR). Of the 9 patients with indolent NHL, 5 patients had PR and 2 patients had stable disease (SD) and remained on study. Of the 9 patients with aggressive NHL, 5 patients had PR (all with mantle cell lymphoma) and 1 patient had SD on study. At data cutoff, the longest duration of response was 9 months in a patient with follicular lymphoma. Enrollment is continuing ([Flinn et al 2009](#)). Kahl and colleagues reported clinical safety and activity in a Phase 1 study of CAL-101 in patients with relapsed or refractory NHL. At data cutoff, the study had enrolled 55 patients with NHL; 28 patients had indolent NHL: FL n=15, small lymphocytic lymphoma n=6, Waldenstrom's macroglobulinemia n=4, marginal zone lymphoma n=3, and 27 had aggressive NHL: MCL n=18, DLBCL n=9. Patient characteristics included 69% males (38 vs. 17 females); median age [range] of 68 [32-82] years, 44% with refractory disease and 56% with relapsed disease. Symptomatic adverse events were infrequent, usually low-grade, and not clearly CAL-101-related. Grade ≥ 3 hematological laboratory abnormalities included neutropenia n= 5 (9%); lymphopenia n=3 (5%), and thrombocytopenia n=3 (5%) with uncertain relationship to CAL-101. Grade ≥ 3 ALT/AST elevations occurred in 18 (33%) patients with onset 2-8 weeks after CAL-101 initiation and resolution 2-4 weeks after CAL-101 interruption. Partial responses were observed at all dose levels, with respective overall n/N (response rates) in evaluable patients of 15/24 (63%) for indolent NHL, 10/16 (62%) for MCL and 0/9 (0%) for DLBCL. Respective response rates, by relapsed or refractory status were 9/13 (69%) and 6/11 (55%) for indolent NHL and 8/11 (73%) and 2/5 (40%) for MCL. 5 Patients have had response durations of ≥ 6 months with response durations ranging to >16 months. The median [range] duration of response was 3 months [1 month to 8 months] in MCL ([Kahl et al 2010](#)).

SAR245409 (S09) was another potent orally administered inhibitor of pan class I PI3K isoforms (alpha, beta, gamma, and delta) and mTOR. In a Phase I dose expansion cohort study, patients with refractory or relapsed lymphomas were enrolled in a lymphoma-specific expansion cohort to receive SAR245409 orally. The duration of each cycle was 28 days. Tumor response was assessed every 8 weeks. Sixteen patients with NHL were enrolled: MCL n=6, FL n=5, DLBCL n=2, HD n=1, follicular transformed lymphoma n=1, and anaplastic T-cell/null cell lymphoma n=1. There were 12 males/4 females with a median age of 69 years (range, 20-90). Among 15 patients, 10 (66.7%) had received 3 or more prior regimens. The most common related adverse events ($> 10\%$ of patients) were nausea (25%), diarrhea (12.5%), and elevated liver enzymes (ALT 18.8% and AST 18.8%). Drug-related grade ≥ 3 ALT elevation occurred during the second cycle in 2 patients (12.5%) and resolved with drug discontinuation. This study is ongoing ([Papadopoulos et al 2011](#)).

Additionally, pan class I PI3K inhibitors have been evaluated in Phase I trials with several demonstrating an acceptable safety profile while stabilizing the disease, even in patients whose disease has been refractory to multiple lines of treatment ([Bendell et al 2012](#), [Von Hoff et al 2011](#), [Chiorean et al 2009](#)).

mTOR, a kinase downstream of PI3K, has emerged as important therapeutic target for cancer treatment. The mTOR inhibitors, temsirolimus and everolimus, have been extensively tested as single agents and found to have activity in lymphoma. A phase-II study of temsirolimus (CCI-779) in patients with relapsed mantle cell lymphoma showed a 44% response rate and demonstrated clinical activity in a variety of NHL subtypes (Smith et al 2010). Similarly, a phase-II study with the oral mTOR inhibitor everolimus has demonstrated activity in NHL, reporting an overall response rate of 30% (range from 30 to 38% depending on NHL types), with a median duration of response 5.7 months (Witzig et al 2011).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of BKM120

NVP-BKM120 (BKM120) is a potent and highly specific oral pan-class I PI3K inhibitor that is a 2,6-dimorpholino pyrimidine derivatives. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacodynamics

BKM120 inhibits wild-type PI3K α (IC₅₀: 35 nM), with at least 50-fold selectivity towards this target compared to other protein kinases as well as against somatic PI3K α activating mutants (H1047R-, E542K-, and E545K-p110 α), the other three PI3K paralogs as well as the direct downstream effector AKT. BKM120 does not inhibit the related kinases, mTOR, or Vps34, nor does it inhibit other receptors and ion channels profiled (IC₅₀ >10 μ M).

BKM120 demonstrates significant tumor growth inhibition in relevant tumor xenografts in mice and rats when administered orally, including models of renal cell cancer (RENCA, 786-0, Caki-1), glioblastoma multiforme (U87MG), prostate cancer (PC3M), lung cancer (A549, NCI-H1975), ovarian cancer (A2780), colorectal cancer (HCT116, HCT-15) and melanoma (A2058, A375). *In vivo* PK/PD analyses of tumor tissues shows a good correlation between exposure, PI3K pathway blockade (S473P-Akt levels), and anti-tumor activity.

1.2.1.1.2 Nonclinical pharmacokinetics and metabolism

BKM120 showed favorable pharmacokinetic properties in all animal species tested. The absorption of [¹⁴C]-BKM120-related radioactivity was >84% in the rat. Oral bioavailability was high in rats (73%), was complete in dogs, and was moderate in monkeys (42%). The estimated steady state plasma volume of distribution (V_{ss}) was high (3.0-3.5 L/kg) in all species tested, suggesting a wide tissue distribution. BKM120 was found to cross the blood brain barrier in rats with a tissue-to-plasma ratio of approximately 2 (Novartis internal data). BKM120 is moderately bound to plasma protein in all species examined (about 80%).

In vitro metabolism studies using human liver microsomes showed that oxidative phase I metabolism of BKM120 was predominantly mediated by CYP3A4 (estimated fm > 0.9). Formation of a BKM120 N-glucuronide conjugate (Phase II metabolism) via the UDP-glucuronosyltransferase-1 family, polypeptide A4 (UGT1A4) was also observed in human

liver microsomes supplemented with uridine 5'-diphospho-glucuronic acid (UDPGA). BKM120 and metabolites have a low potential for covalent binding to protein.

BKM120 was determined to be a weak reversible inhibitor of CYP3A4 ($IC_{50} = 8 \mu M$, $K_i = 13.4 \mu M$ unbound) at concentrations reached in the clinic. BKM120 very weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC_{50} values ranging from 35-65 μM (34-59 μM unbound). BKM120 did not show time-dependent inhibition of CYP450 enzymes. In GLP toxicology studies, BKM120 exposure in terms of AUC_{0-24h} and C_{max} increased in a dose proportional manner in rat and dog. Results from the rat ADME study showed that radioactivity was mainly excreted into the feces. Renal excretion was minor. There was no noticeable drug accumulation in dog or male rats after 13 weeks of daily dosing. There was a slight accumulation in female rat (< 2 fold).

Further information concerning the pharmacokinetic and pharmacodynamics properties of BKM120 may be found in the [Investigator's Brochure].

1.2.1.1.3 Safety pharmacology and toxicology

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted in vitro and in vivo did not indicate a prominent electrophysiological risk. No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, which was observed in two dog telemetry studies. In rats and dogs, clinical pathology and histopathology findings showed quantitative reductions of lymphoid and erythroid counts and lymphoid tissue hypoplasia.

The pancreas was seen to be affected by treatment with BKM120, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. At higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both the endocrine as well as the exocrine pancreas.

Male sexual organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatid giant cells and abnormal spermatids, and cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats (highest dose), although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles. In dogs, there was no effect on female sexual organs.

Glucose homeostasis was affected in various species (mice, rats, dogs), as expected from the mode of action of BKM120. However, these effects were minimal in both rats and dogs at the doses used in the 4-week studies.

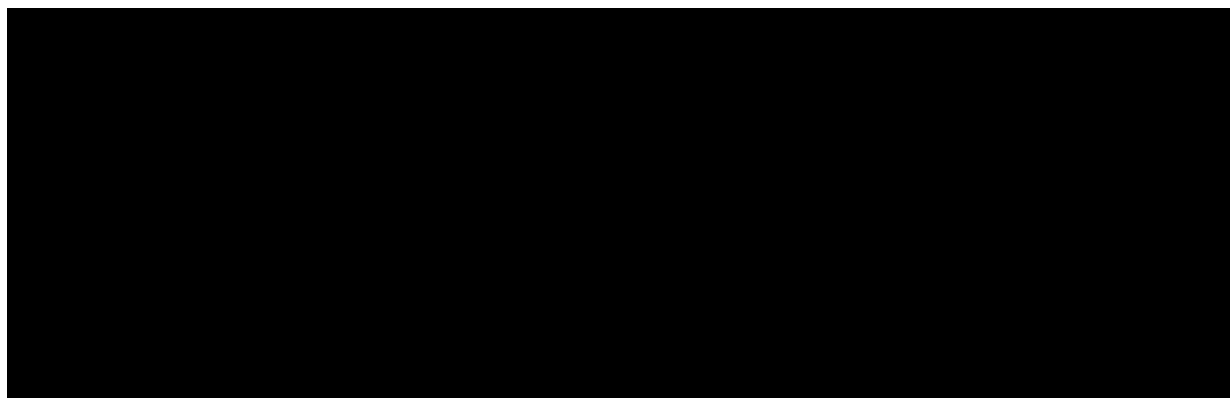
Other safety considerations include:

- After up to 2 weeks of treatment with up to 2.5 mg/kg/day of BKM120, alterations in the levels of multiple brain neurotransmitters were seen in rats.
- No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with BKM120. However, evidence of a genotoxic potential with BKM120 has been seen in vitro and in vivo and is likely due to an aneugenic effect.

- No phototoxic potential or any effect on wound healing has been identified with BKM120 in pre-clinical studies.

In conclusion, the majority of the observed effects were related to the pharmacological activity of BKM120 as an inhibitor of PI3K, such as a potential influence on glucose homeostasis and the risk of increased blood pressure.

Please refer to the [Investigator's Brochure] for additional information on the preclinical testing of BKM120.



1.2.1.2 Clinical experience

As of September 2011, a total of 251 patients were enrolled into eight Novartis sponsored clinical studies of BKM120 for oncology indications other than NHL:

- Phase I single agent studies [CBKM120X2101] (First in man dose escalation in solid tumors) and [CBKM120X1101] (Japanese dose escalation in solid tumors)
- Phase II single agent studies [CBKM120C2201] (endometrial cancer) and [CBKM120D2201] (non-small cell lung cancer)
- Phase I combination studies [CBKM120B2101] (BKM120 plus GSK1120212), [CBKM120X2107] (BKM120 plus trastuzumab), [CBEZ235A2118] (BKM120 plus paclitaxel), and [CMEK162X2101] (BKM120 plus MEK162).

1.2.1.2.1 Human safety and tolerability data

Study recruitment in study [CBKM120X2101] has been completed with forty (40) patients included in the dose escalation phase at 6 dose levels (all once daily) (12.5 mg (1 patient); 25 mg (2), 50 mg (5), 80 mg (11), 100 mg (17), 150 mg (4)) (Bendell et al 2012). Dose limiting toxicities were hyperglycemia, skin rash, epigastric pain, mood disorder, joint pain. The MTD for BKM120 given as single agent, once daily was established at 100 mg/day. Forty-three additional patients were treated in the expansion cohort at 100 mg/day. At the cut-off date of 4-Jul-2011 patient characteristics of 82 patients analyzed were as follows: median age 55 years (range 30–78); ECOG performance status 0/1/2 for 35/46/1 patients, respectively. The safety experience for this single agent trial of BKM120 is described in Table 1-1.

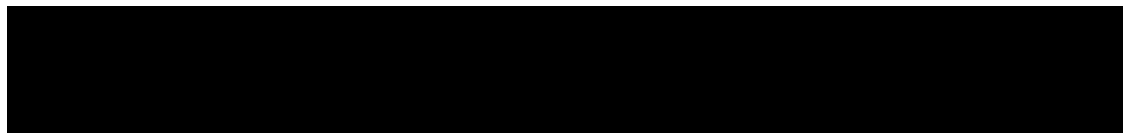


Table 1-1 Most frequent AEs (at least 15%) related to study drug in study CBKM120X2101 (n=81):

Event	All grades	Grade 3/4
Fatigue/asthenia	31(38.3%)	3 (3.7%)
Decreased appetite	24 (29.6%)	-
Diarrhea	24 (29.6%)	3 (3.7%)
Hyperglycemia	24 (29.6%)	4 (4.9%)
Nausea	24 (29.6%)	-
Rash	22 (27.2%)	4 (4.9%)
Mood altered/emotional disorder/affective disorder	17 (21.0%)	4 (4.9%)
Transaminases increased	16 (19.8%)	9 (11.1%)
Anxiety	14 (17.3%)	1 (1.2%)
Depression	14 (17.3%)	1 (1.2%)

A second single agent trial, [CBKM120X1101] was a phase I dose escalation study in Japanese patients with advanced solid tumors with dose levels ranging from 25 to 100 mg/day (Doi et al 2011). Enrolment of 15 patients has been completed, including 9 patients at 100 mg/day. One DLT (G4 hepatic function abnormal) was observed in the 100 mg/day group. The most common G3 or G4 adverse events occurring in at least 2 patients were hepatic function abnormal in 6 patients including transaminase increase in 2 patients, G3 anemia in 2 patients, hypokalemia in 2 patients. The recommended phase 2 dose (RP2D) for Japanese has been determined at 100 mg/day, as in the western population.

BKM120 in combination with trastuzumab is currently investigated in a phase Ib/II [CBKM120X2107] study in patients with HER2-positive MBC who acquired trastuzumab resistance. The phase Ib part of the study has been presented (Saura et al 2011). In this study trastuzumab is given at fixed dose of 2 mg/kg/week (with a 4 mg/kg/week loading dose). In the dose escalation phase, 17 patients with MBC have been enrolled at the cut-off date of September 30th, 2011: 5 patients at 50 mg/day and 12 patients at 100 mg/day. The recommended phase 2 dose for BKM120 was declared at 100 mg/day. The median age was 47 years (range 28 -70). Most of the patients have been heavily treated (range of prior chemotherapy lines 1-8). With the completion of escalation phase, BKM120 in combination with trastuzumab has shown an acceptable safety profile. Grade 3 adverse events reported with a suspected relationship to BKM120 were asthenia, ALT increase, hypersensitivity hyperglycemia, mood altered, affective disorder, photosensitivity reaction and rash in 1-2 patients each. No drug related G4 toxicity has been observed so far. The trial is currently recruiting the phase II part.

Details on liver toxicity, mood alterations, pneumonitis and hyperglycemia as side effects of BKM120 are presented below.

Please refer to [BKM120 Investigator's Brochure] for more detailed information on specifics of clinical safety and tolerability of BKM120.

Liver Toxicity

Approximately 25 to 45% of patients treated with single agent BKM120 reported liver toxicity (all grades, regardless of study drug relationship, 100 mg/d dose) based on a search of multiple MedDRA event terms (e.g. SMQ preferred terms). The incidence of grade 3 and 4 events was approximately 10 to 30%. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). Data suggest a slightly higher rate of grade 3 and 4 liver enzyme elevations in Japanese patients (44%) in the [CBKM120X1101] study, however, the number of patients treated at 100 mg in this study was limited (n=9). Transaminase elevations typically occur during the first 6 to 8 weeks of treatment start.

Although transaminase increases are relatively common, only a few of the patients had other simultaneous observations related to impaired liver function (e.g. bilirubin increase or clinical symptoms).

Based on these findings, conservative inclusion criteria and guidelines to monitor and follow patients with LFT alterations (including dose and schedule modifications) have been implemented. Please refer to the respective inclusion/exclusion criteria and [Section 5](#) in this protocol for more detailed guidelines.

A recent liver safety review across Novartis-sponsored trials with BKM120 identified several potentially drug-induced liver toxicity (DILI) cases (e.g. AST/ALT >3.0 x ULN and TBL >2.0 x ULN at any time during the treatment, regardless of causality. Upon medical review, most of these cases occurred in the context of disease progression in terminally ill, advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT >3.0x ULN and TBL >2.0xULN in the absence of cholestasis and other explanatory causes) with probable causal relationship to study treatment. Five of these cases were enrolled in study [CBKM120F2302] in combination with fulvestrant, and one in combination with the investigational drug LDE225 (sonidegib). All patients have recovered upon treatment discontinuation except one patient for whom no data is available since the patient refused to return for safety follow-up.

Mood alteration

Recently, a number of publications demonstrated that the modulation of AKT/GSK3 signaling pathway by neurotransmitters is important for the regulation of behavior ([Beaulieu et al 2009](#)). Preclinical studies conducted in rats to investigate the effect of BKM120 on different neurotransmitters have shown that repeated administration of BKM120 resulted in an enhanced decrease in glutamate, dopamine, serotonin and epinephrine as well as in an enhanced increase in GABA and HIAA.

Reversible mild to moderate mood disorders observed at 100 mg/day, regardless of study drug relationship, in ongoing BKM120 studies are summarized in [Table 1-2](#).

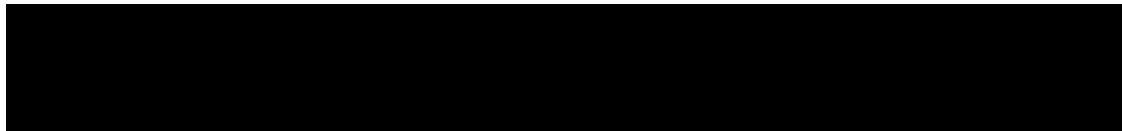


Table 1-2 Numbers of patients with mood disorders occurred at 100 mg/day in ongoing BKM120 studies

Study Number (N= patient treated with 100 mg/d BKM120)	All grades	Grade3/4
CBKM120X2101 (N = 55)	11 (20%)	2 (3%)
CBKM120X1101 (N = 9)	4 (44%)	0 (0%)
CBKM120C2201 (N = 50)	6 (12%)	0 (0%)
CBKM120X2107 (N = 12)	7 (58%)	2 (16.7%)
CBEZ235A2118 (N = 6, BKM120 treated only)	0 (0 %)	0 (0%)

These adverse events are currently under investigation. Nevertheless, until a more complete understanding of this AE is compiled and in order to lower the risk, protocol guidelines disqualify patients with an active and/or history of major psychiatric disorder. In addition, throughout the trial patients must be closely monitored using self-rating questionnaires (i.e. PHQ-9 and GAD-7), when required a psychiatrist should be consulted and the use of standard available medication should be considered as per investigator's discretion. Detailed instructions are provided in [Section 7](#).

Across the ongoing studies of BKM120, 4 patients experienced other psychiatric toxicities related to BKM120: confusional state in 3 patients (grade 3 in 1 patient) and mental status change in 1 patient (grade 3). With regards to the confusional state, in one case it has been considered as a symptom related to mood disorders, cholangitis and brain metastases, and in the remaining two cases, the confusional state occurred in a context of infection and gastrointestinal disorders. In two out of the three cases, the event improved/resolved after study drug interruption. Further information is being collected for the latest reported case.

Lung Toxicity/Pneumonitis

Lung changes compatible with pneumonitis have not been observed in the preclinical setting. Among the current studies, lung toxicity has been observed in 2 patients and reported as pneumonitis, including a fatal outcome reported in one patient in a complex clinical context, combining progression of lung lesions and aspergillosis infection. The currently available data do not enable a clear assessment about the causal relationship of pneumonitis with BKM120 treatment. Newly appearing or significant changes in pulmonary symptoms (which cannot be explained by the underlying disease), should be carefully followed with appropriate management as per institutional guidelines and the guidelines provided in the protocol.

Hyperglycemia events

The PI3K/Akt pathway plays a significant role in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered as an "on target" effect of BKM120. Regular monitoring of insulin C-peptide is implemented in BKM120 protocols to evaluate this pharmacodynamics effect. Transient increases of plasma glucose levels have been reported commonly in patients treated with BKM120. Hyperglycemia observed at 100 mg/day, regardless of study drug relationship, in ongoing BKM120 studies are summarized in [Table 1-3](#).

Table 1-3 Number of patients with hyperglycemia occurred at 100 mg/day in ongoing BKM studies

Study Number (N= patient treated with 100 mg/d BKM120)	All grades	Grade3/4
CBKM120X2101 (N = 55)	17 (30.9%)	2 (3.6%)
CBKM120X1101 (N = 9)	2 (22.2%)	1 (11.1%)
CBKM120C2201 (N = 50)	31 (62.0%)	12 (24.0%)
CBKM120X2107 (N = 12)	4 (33.3%)	2 (16.7%)
CBEZ235A2118 (N = 6, BKM120 treated only)	2 (33.3%)	1 (16.7%)

The highest rate of hyperglycemia (62.0%) was reported in [CBKM120C2201], a phase II study conducted in patients with advanced endometrial carcinoma, as this was the only study among those listed allowing the enrollment of patients with controlled diabetes mellitus. However, so far, there were only two patients that experienced a grade 4 hyperglycemia, and they both were treated at the highest dose level (150mg/day) in [CBKM120X2101] study. Detailed guidelines to monitor and manage patients who develop hyperglycemia are provided in Table 6-3. Specifically, with regards to appropriate concomitant medication, considering that *in vitro* studies have shown that BKM120 may inhibit insulin-stimulated glucose uptake, the first recommended approach is to use oral anti-diabetics (e.g. metformin) who increases muscle and fat glucose uptake. The addition of insulin can be considered based on the guidelines of American Diabetes Association included as reference in the current protocol.

1.2.1.2.2 Human pharmacokinetic and metabolism data

Preliminary clinical pharmacokinetic data of BKM120 after single and multiple daily dosing is available from the first-in-human trial [CBKM120X2101]. BKM120 was administered as a capsule (doses ranging between 12.5 and 150 mg) and full pharmacokinetic profiles were collected on Day 1, Day 8 and Day 28 of Cycle 1.

BKM120 was rapidly absorbed, with the median time to reach the peak plasma concentration (T_{max}) ranging from 1.0 to 1.75 hours following administration. T_{max} was independent of dose and was not altered after multiple oral doses. Variability in systemic drug exposure was moderate at all dose levels. At 100 mg the variability in systemic drug exposure and C_{max} (CV %) at steady-state was moderate, about 36% and 25%, respectively.

During once daily dosing, plasma BKM120 concentrations were found to accumulate in reaching steady-state. After one week of oral daily dosing (day 8), both C_{max} and AUC_{0-24h} were approximately 3-fold higher than after a single dose (day 1). The mean accumulation ratio (R_{acc}) of BKM120 at 100 mg was 2.7 and 3.3 on days 8 and 28, respectively, indicating the absence of significant drug accumulation after day 8.

The decay in BKM120 plasma concentration over time was bi-exponential, with an apparent long terminal half-life. The mean T_{1/2,acc} (effective half-life, obtained from drug accumulation) calculated from exposure data at day 28 ranged between 38 and 49 hours across all dose levels. T_{1/2,acc} was found to be independent of dose. Based on the effective half-life, steady state BKM120 plasma levels can be expected to be reached after 1 week of daily dosing.

Furthermore the preliminary PK data within the Japanese population [CBKM120X1101] show no significant differences in C_{max} or AUC_{0-24h} with the Caucasian population [CBKM120X2101]. A preliminary population PK analysis, including data from studies [CBKM120X2101] and [CBKM120X1101] confirmed those findings (Novartis internal data).

1.2.1.2.3 Clinical efficacy data

BKM120 has not been tested in patients with NHL to date. The following information comes from the Novartis sponsored clinical trials for solid tumors.

Sixty six patients were evaluable for response in study [CBKM120X2101] where all patients in the expansion cohort were required to have mutated and/or amplified PIK3CA and/or mutated PTEN or null/low PTEN protein expression: partial tumor responses (PR) were observed in 3 patients, one of which was a RECIST v1.0 confirmed PR in a patient with triple negative breast cancer and the other 2 not confirmed (1 patient with metastatic breast cancer and 1 patient with parotid carcinoma) (Graña et al 2011).

The first patient was a [REDACTED] with poorly differentiated ductal metastatic breast cancer assessed as triple negative (ER-, PgR-, HER2-), PI3KCA wild type, PTEN IHC positive. Since [REDACTED] received many previous anticancer agents (cyclophosphamide, doxorubicin, gemcitabine, docetaxel, paclitaxel, vinorelbine, capecitabine, etoposide, anastrozole). As progressive disease developed (bulky lymph node involvement and local breast relapse), [REDACTED] was enrolled [REDACTED] in the Phase I study of BKM120 in the 100 mg/day cohort. A metabolic response ([REDACTED] decrease in SUV) was observed after 2 cycles, followed by a RECIST partial response ([REDACTED] tumor shrinkage) after 4 cycles. This patient continues to receive treatment beyond 32 cycles.

The second patient was a [REDACTED] with moderately differentiated ductal metastatic breast cancer, assessed as ER positive, HER2 negative, PI3KCA mutated (E545K & H1047Y), PTEN IHC positive. [REDACTED] had been previously treated with several antineoplastic agents. When [REDACTED] received BKM120 at 100 mg/day [REDACTED], [REDACTED] had measurable metastases in the brain, lung and liver. At the second radiological assessment after receiving 4 cycles of BKM120 treatment, a [REDACTED] reduction of the sum of the lesions was recorded. The TTP for this patient was 24 weeks.

The third patient was a [REDACTED] with grade 4 parotid gland ductal carcinoma, PI3KCA wild type, PTEN IHC positive. [REDACTED] had been previously treated with doxorubicin and adriamycin. After disease progression was observed on this regimen [REDACTED] was enrolled in the 100mg/day cohort [REDACTED] in the [CBKM120X2101] study. At the first radiological assessment after receiving 2 cycles of BKM120 treatment, a [REDACTED] reduction of the sum of the lesions was recorded. The TTP for this patient was 16 weeks.

As of the data cut-off 4-Jul-2011, preliminary analysis shows forty-five percent of patients (30 of 66 evaluable) had stable disease as best response, with 20 patients (30%) with a disease stabilization of 3 months or longer. A trend towards better activity (long-term stabilizations) has been observed at the higher dose cohorts, also expressed in metabolic FDG-PET response. However, considering the impact of a PI3K inhibitor on glucose metabolism, further data needs to be acquired to understand whether the current FDG-PET assessment data can be used as a predictive factor for efficacy.

[REDACTED]

With regards to pharmacodynamic markers observed in study [CBKM120X2101], down regulation of pS6 in skin by 30-80% was demonstrated in 28 out of the 38 evaluable patients at 100 and 150 mg/d and more than 25% FDG-PET signal decrease in patients at doses greater than the MTD.

With regards to the PI3K pathway activation, of the two responders described above, one had a tumor with the PIK3CA mutation. Moreover, 18 patients had a stable disease lasting for 16 weeks or longer, including 8 patients who had tumors with an activated PI3K pathway. These data are promising and continued exploration of the activity of BKM120 in patients with activated PI3K pathway is warranted.

Pharmacokinetic experience

Preliminary PK data showed that at the low dose of 40 mg on both days 8 and 22 of treatment, the PK of BKM120 in this study was consistent with that seen following single agent administration of BKM120. At the 80 mg dose, observed profiles on days 8 and 22 were slightly lower than expected (less than 10%). At the other 2 dose levels (60 mg and 100 mg) almost all of the profiles lie in the lower half of the expected distribution indicating a large reduction (around 30%) in exposure to BKM120 compared to expectations. Hypotheses explaining this observation are being evaluated. These include: a possible impact of H2 antagonist administration as premedication for paclitaxel, which could limit BKM120 solubility (i.e., BKM120 exhibits pH-dependent solubility, with a significant increase in solubility at low pH) or more likely an interaction between this and the extremely rapid absorption kinetics of BKM120 (half-life of 10 minutes) suggesting a limited window for absorption in the upper part of the duodenum. To limit the potential impact of H2 antagonists, in this study BKM120 will be administered at least one hour before H2 antagonists (or proton pump inhibitor, antacid, etc.) administration.

2 Rationale

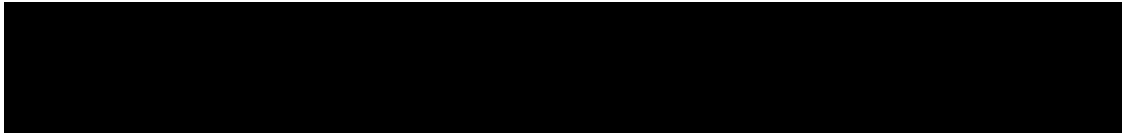
2.1 Study rationale and purpose

The PI3K/Akt/mTOR pathway has become an important focus for cancer therapeutics.

BKM120 is a potent and highly specific oral pan-class I PI3K inhibitor and has been studied extensively in non-clinical models and is currently being evaluated in clinical trials for several oncology indications other than NHL to date (see details in [Section 1.2](#)).

As already stated in the previous sections, inhibitors of the PI3K/mTOR/Akt pathway, including BKM120, may be therapeutically effective in NHL patients based on the observations from both pre-clinical and early phase clinical trials with either selective or non-selective inhibitors of the PI3K/mTOR/Akt pathway. As pan class I PI3K inhibitors demonstrate evidence of efficacy in solid tumor patients and since there are several p110 isoforms detected in B cell NHLs, this presents an intriguing opportunity for further evaluation of BKM120. Therefore, there is a strong rationale to support this study of BKM120 for the selected types of B-cell NHL.

The purpose of this study is to explore therapeutic efficacy of BKM120 in three selected types of NHL, including DLBCL, MCL and FL, and the safety/tolerability of patients.



2.2 Rationale for the study design

An open-label, multi-center, single arm phase II study has been selected to explore the efficacy and safety of BKM120 in patients with three histologically different relapsed/refractory non-Hodgkin's lymphomas, including diffuse large B-cell lymphoma, mantle cell lymphoma and follicular lymphoma.

No clear data exist on the effect of molecular alteration and data with PI3K/mTOR inhibitor do not currently support the notion of a specific target population. Thus, enrollment of patients with activated as well as non-activated PI3K pathway is considered appropriate.

In the absence of a comparator arm and robust historical data, ORR is considered an appropriate primary endpoint to objectively measure anti-tumor activity.

A single arm study will be performed due to the lack of approved agents as well as the small patient population.

The protocol specific assessments, treatment and follow-up are consistent with the standard procedures applied in this disease setting.

2.3 Rationale for dose and regimen selection

As described in details in [Section 1.2.1.2.1](#), BKM120 100 mg once daily has been established as the MTD/RP2D in two single agent trials ([\[CBKM120X2101\]](#) and [\[CBKM120X1101\]](#)) and one combination trial ([\[CBKM120X2107\]](#) with trastuzumab).

Accordingly, BKM120 will be dosed at 100 mg/day.

2.4 Rationale for choice of combination drugs

Not applicable.

2.5 Rationale for choice of comparators drugs

Not applicable.

3 Objectives and endpoints

Objectives and related endpoints are described in [Table 3-1](#) below.

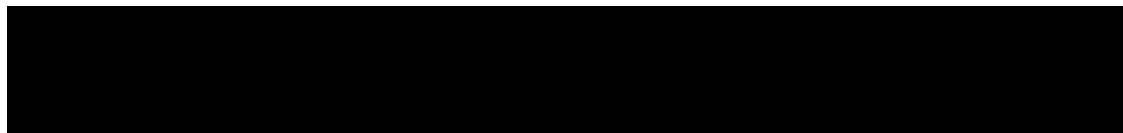
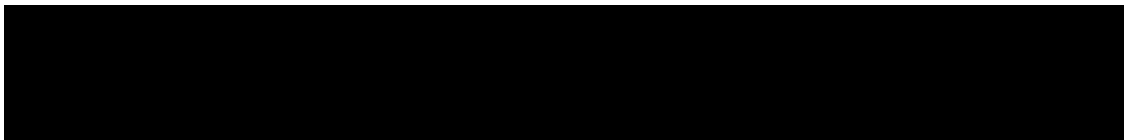
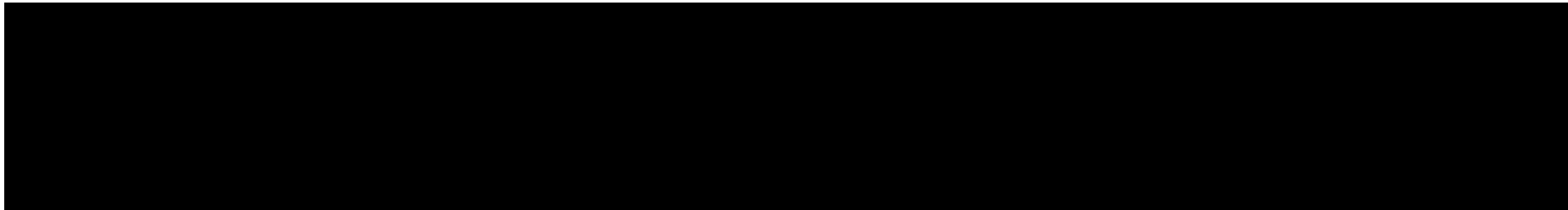


Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary - To determine the efficacy of BKM120 in patients with relapsed/refractory Non-Hodgkin Lymphoma in the three different histological subgroups (cohorts)	Overall Response rate (ORR) is defined as the proportion of patients with a best overall response of CR or PR according to Cheson criteria (Cheson et al 2007).	Refer to Section 10.4
Secondary - To evaluate the safety and tolerability in the three different histological subgroups - To assess progression free survival in the three different histological subgroups - To assess the duration of response in the three different histological subgroups - To assess overall survival in the three different histological subgroups	Frequency and severity of adverse events; other safety data as considered appropriate Progression Free Survival (PFS) is defined as the time from the date of treatment start to the date of the first documented progressive disease (PD) or death due to any cause per local investigator. Duration of Response is defined as the time from the date of first occurrence of CR or PR to the date of the first documented progressive disease (PD) or death due to lymphoma. Overall Survival (OS) is defined as the time from treatment start to the date of death due to any cause.	Refer to Section 10.5

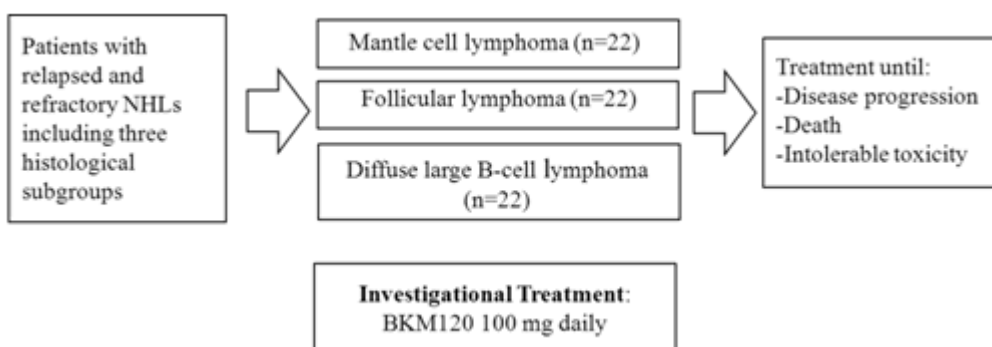


4 Study design

4.1 Description of study design

This is a multi-center, open label, single arm phase II study in patients with relapsed and refractory Non-Hodgkin Lymphoma including 3 histological subgroups (cohorts): mantle cell lymphoma (MCL), follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). A study design overview is given in Figure 4-1.

Figure 4-1 Study Design Overview



Note: Maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment.

Screening

Patient must provide a signed Informed Consent Form (ICF) prior to any study specific screening evaluations. Eligibility will be determined according to the inclusion/exclusion criteria as detailed in [Section 5](#). A list of procedures to be performed at screening is summarized in [Table 7-1](#). Patients must meet all eligibility criteria to be considered for enrollment in the study.

Treatment and monitoring

Treatment will be organized into cycles of 28 days in all cohorts and patients will receive daily BKM120 from Day 1 in Cycle 1, and continue until disease progression, intolerable toxicity or withdrawal of consent, or until other criteria for discontinuation are met, whichever comes first.

Patients will return to the clinic for regular safety and efficacy assessment as outlined in [Table 7-1](#). At each office visit, remaining study drug should be accounted for to allow assessment of patient treatment adherence.

Study treatment duration is determined independently for each cohort. Response to treatment will be determined locally according to Cheson criteria ([Cheson et al 2007](#)) every 8 weeks until disease progression or until 6 months after the last patient in that cohort has started the study treatment, whichever comes first. All patients benefiting from treatment at the time of

final analysis will be permitted to continue study drug at investigator's discretion until disease progression, intolerable toxicity or withdrawal of consent.

An end of treatment visit will occur within 7 days following discontinuation of BKM120.

Safety follow-up

After discontinuation of study treatment, patients will be followed for safety (AEs and/or SAEs) for at least 30 days.

Efficacy follow-up

Patients who discontinue from BKM120 for other reasons than disease progression, lost to follow up, death, or withdrawal of consent will continue to have tumor assessments every 8 weeks in each cohort until disease progression, start of new anticancer therapy, lost to follow up, death, withdrawal of consent or until 6 months after the last patient in that cohort has started the study treatment, whichever comes first. All new anticancer therapies given after the last dose of the study drug will be recorded on Case Report Forms (CRFs) designed to capture antineoplastic therapies since discontinuation from the study.

Survival follow-up

All patients will be followed for survival outcome after they discontinue from study treatment and tumor evaluations (efficacy follow-up). Survival follow-up assessments in each cohort will be performed once every 3 months by either office visits or telephone calls until death, lost to follow-up, withdrawal of consent or until 6 months after the last patient in that cohort has started the study treatment, whichever comes first.

4.2 Timing of interim analyses and design adaptations

Not applicable.

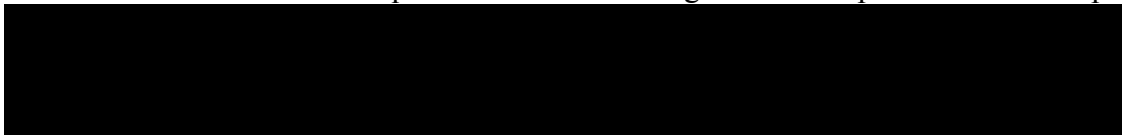
4.3 Definition of completion of the study

The study will end when the treatment period, safety follow-up, efficacy follow-up and survival follow up have ended for all patients as described above, or when a decision is made to terminate the study early.

The main efficacy and safety analysis for each cohort will be performed when all patients included in the corresponding cohort experienced disease progression, discontinued early, or 6 months after the last patient has started the first cycle of treatment, whichever comes first. This is also the time of completion of study treatment for that cohort. An update of the analyses will be conducted after all enrolled patients have completed the study.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patients remaining in the study should be seen as soon as possible and the same assessments should be performed as described in [Section 7](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The



investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The population consists of adult patients with relapsed and refractory mantle cell lymphoma, follicular lymphoma and diffuse large B-cell lymphoma.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient has provided a signed study Informed Consent Form prior to any screening procedure
2. Patient is ≥ 18 years of age on the day of consenting to the study
3. Patient has a histologically confirmed diagnosis of mantle cell lymphoma, follicular lymphoma, or diffuse large B cell lymphoma
4. Patient has relapsed or refractory disease and received at least one prior therapy
5. Patient with diffuse large B cell lymphoma has received or is ineligible for autologous or allogeneic stem cell transplant. This does not apply to patients with mantle cell lymphoma and follicular lymphoma
6. Patient has at least one measurable nodal lesion (≥ 2 cm) according to Cheson criteria ([Cheson et al 2007](#)). In case where the patient has no measurable nodal lesions ≥ 2 cm in the long axis at baseline, then the patient must have at least one measurable extra-nodal lesion
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2
8. Patient has adequate bone marrow and organ function shown by:
 - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$
 - Platelets $\geq 75 \times 10^9/L$ (no platelet transfusion within past 14 days)
 - Hemoglobin (Hgb) ≥ 9.0 g/dL (no RBC transfusion within past 14 days)
 - International Normalized Ratio (INR) ≤ 1.5
 - Potassium, calcium (corrected for albumin), magnesium within normal limits for the institution
 - Serum Creatinine $\leq 1.5 \times$ ULN
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range (or $\leq 3.0 \times$ ULN if liver metastases are present)
 - Serum bilirubin \leq ULN (or $\leq 1.5 \times$ ULN if liver metastases are present; or total bilirubin $\leq 3.0 \times$ ULN with direct bilirubin within normal range in patients with **well documented** Gilbert Syndrome which is defined as presence of several episodes of unconjugated hyperbilirubinemia with normal results from CBC count (including

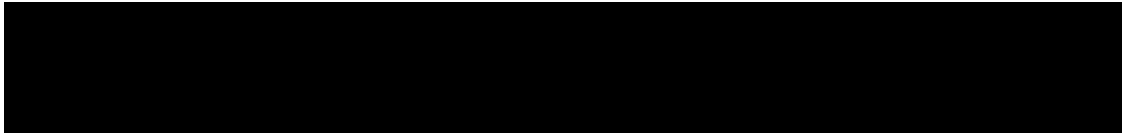
normal reticulocyte count and blood smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis.)

- Fasting plasma glucose (FPG) ≤ 120 mg/dL or ≤ 6.7 mmol/L
9. Patient is able to swallow and retain oral medication

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has received previous treatment with PI3K inhibitors
2. Patient has evidence of graft versus host disease (GVHD)
3. Patient has active or history of central nervous system (CNS) disease
4. Patient has a concurrent malignancy or has a malignancy within 3 years of study enrollment (with the exception of adequately treated basal or squamous cell carcinoma or non-melanomatous skin cancer)
5. Patient has a score ≥ 12 on the PHQ-9 questionnaire
6. Patient selects a response of “1, 2 or 3” to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the response to question 9 or the total score of the PHQ-9)
7. Patient has a GAD-7 mood scale score ≥ 15
8. Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others), or patients with active severe personality disorders (defined according to DSM- IV). For patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug.
9. Patient has \geq CTCAE grade 3 anxiety
10. Patient is concurrently using other approved or investigational antineoplastic agent
11. Patient has received chemotherapy or targeted anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, monoclonal antibodies or mitomycin-C) prior to starting study drug or who have not recovered from side effects of such therapy
12. Patient has received pelvic and/or para-aortic radiotherapy ≤ 28 days prior to enrollment in this study or has not recovered from side effects of such therapy at the time of initiation of screening procedures
13. Patient has had major surgery within 28 days prior to starting study drug or has not recovered from major side effects of the surgery
14. Patient has poorly controlled diabetes mellitus ($\text{HbA}_{1c} > 8\%$) at baseline
15. Patient has active cardiac disease including any of the following:
 - Left Ventricular Ejection Fraction (LVEF) $< 50\%$ as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
 - QTc > 480 msec on screening ECG (using the QTcF formula)
 - Angina pectoris that requires the use of anti-anginal medication
 - Ventricular arrhythmias except for benign premature ventricular contractions

- Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
 - Conduction abnormality requiring a pacemaker
 - Valvular disease with documented compromise in cardiac function
 - Symptomatic pericarditis
16. Patient has a history of cardiac dysfunction including any of the following:
- Myocardial infarction within the last 6 months, documented by persistent elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LVEF function
 - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
 - Documented cardiomyopathy
17. Patient is currently receiving treatment with QT prolonging medication known to have a risk to induce Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug
18. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BKM120 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
19. Patient is currently receiving increasing or chronic treatment (> 5 days) with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (> 5 days) can induce CYP3A4. The following uses of corticosteroids are permitted: single dose, topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
20. Patient has other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment contraindicate his/her participation in the clinical study (e.g. chronic pancreatitis, active chronic hepatitis, immunocompromised, chronic pulmonary disease including dyspnea at rest or interstitial lung disease, uncontrolled hypertension etc.)
21. Patient has a history of non-compliance to medical regimen or inability to grant consent.
22. Patient is currently being treated with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Patients must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment. Note: the oral anti-diabetic drugs troglitazone and pioglitazone are CYP3A inducers. Refer to [Table 14-1 in Appendix 1](#).
23. Patient is currently receiving warfarin or other coumarin derived anti-coagulant for prophylaxis. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
24. Patient has a known history of HIV (testing not mandatory) infection
25. Patient has acute viral hepatitis or a history of chronic or active HBV or HCV infection, (typically defined by elevated AST/ALT (persistent or intermittent), high HBV DNA level, HBsAg positive, or high HCV RNA level (testing not mandatory, refer to [Section 7.2.2.5.8](#)))
- 

26. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum hCG laboratory test (> 5 mIU/mL)
27. Patient who does not apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment

Female Patients

- **Women of child-bearing potential**, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through 4 weeks after the final dose of study treatment

Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study subjects, the vasectomized male partner should be the sole partner for that patient]
- Use a combination of the following:
 - a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Note: Hormonal contraception methods (e.g. oral, injected, implanted) are not allowed as it cannot be ruled out that BKM120 decreases the effectiveness of hormonal contraceptives.

- **Women are considered post-menopausal and not of child bearing potential** if any of the following conditions is fulfilled:
 - Prior bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago
 - Age ≥ 60
 - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy), and FSH and estradiol in the postmenopausal range (serum FSH > 40 mIU/mL and estradiol < 20 pg/mL or according to the postmenopausal range definition for the laboratory involved).

Male Patients

- Fertile males, defined as all males physiologically capable of conceiving offspring must use a highly effective contraception during dosing of the study agent - contraception through 16 weeks after final dose of study therapy and should not father a child in this period. Female partner of male study subject: highly effective

contraception during dosing of the study agent - contraception through 16 weeks after final dose of study therapy

28. Patient who has a known hypersensitivity to any of the excipients of BKM120

6 Treatment

6.1 Study treatment

The investigational or study drug to be used in the course of this trial is BKM120. Novartis Drug Supply Management or its designee will provide BKM120 as 10-mg, and 50-mg hard gelatin capsules as individual patient supply, packaged in bottles. BKM120 will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area. The investigator needs to instruct the patient to take the study drug as per the protocol. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded in the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

BKM120 100 mg will be administered orally once daily on a continuous dosing schedule. A complete treatment cycle is defined as 28 days of once daily continuous treatment with BKM120.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
BKM120	Oral gelatin capsules	100 mg	Daily (28 day cycles)

6.1.1.1 BKM120 Administration

BKM120 will be administered on a continuous once daily dosing schedule. There will be no breaks between dosing cycles.

The following general guidelines should be followed for BKM120 administration:

- Patients should be instructed to take the dose of BKM120 once daily in the morning, at approximately the same time each day.
- BKM120 can be taken with or without food.
- BKM120 should be taken with a glass of water. Patients should swallow the capsules as a whole and not chew them.
- To limit the potential impact of H2 antagonists, in this study BKM120 will be administered at least one hour before or 10 hours after H2 antagonists (or proton pump inhibitor, antacid, etc.) administration.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- If the patient forgets to take her dose before 18:00 (6:00 PM), then the dose should be withheld that day and BKM120 should be restarted the following day.

- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (*Citrus X sinensis*) juice is allowed.
- Patients must avoid concomitant intake of strong and moderate CYP3A inhibitors and inducers. Detailed information on potential drug interactions and a list of prohibited concomitant CYP3A interfering medications is provided in [Table 14-1](#) in [Appendix 1](#).

6.1.2 Ancillary treatments

For more information about handling diarrhea, rash, hyperglycemia and pneumonitis see [Section 6.3](#).

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

In general, patients will be treated until disease progression or unacceptable toxicity. Guidance for continuation of study treatment in case of toxicity (e.g. dose delay and/or modification) is provided in [Section 6.3](#).

6.1.5 Treatment duration

Patient will be treated until disease progression, death, unacceptable toxicity or other discontinuation criteria are met. One cycle equals 28 days.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modification

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in BKM120 administration must be recorded on the eCRF.

BKM120 dose modification guidelines are described in [Section 6.3.2.1](#). Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle.

If the administration of BKM120 is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose. The same applies if the patient

experienced an unacceptable toxicity not specifically described in [Table 6-3](#) or [Section 6.3.2](#), provided this toxicity resolved to \leq CTCAE grade 1, unless otherwise specified.

6.3.2 Treatment interruption and treatment discontinuation

If the study drug is being held due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the held study drug), as described in [Table 7-1](#). Additional exams may be required as outlined in [Table 6-3](#), or as medically indicated.

If treatment with the study drug is held for ≥ 28 days due to toxicity, then study drug must be permanently discontinued. Patients who permanently discontinue the study drug should have weekly follow-up for 30 days after discontinuation of all study treatment or resolution of the AE to \leq grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

6.3.2.1 Criteria for BKM120 dose modifications

For each patient, a maximum of 2 dose reductions (as outlined in [Table 6-2](#)) will be allowed. Patients requiring an additional dose reduction will be discontinued from treatment with BKM120.

Table 6-2 Dose reduction steps for BKM120

BKM120 dose levels and dose reductions*	
Starting dose level – 0	100 mg/day
Dose level – 1	80 mg/day
Dose level – 2	60 mg/day

*Dose reduction should be based on the worst preceding toxicity

Guidelines for dose modification and dose interruption for toxicities suspected to be related to BKM120 are described in [Table 6-3](#).

After treatment is resumed at a lower dose:

- If the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.
- These stipulations do not apply to hyperglycemia, as specific rules are stated in [Table 6-3](#).

Table 6-3 Criteria for interruption and re-initiation of BKM120 treatment

These changes must be recorded on the Dosage Administration Record CRF

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - $1.5 \times 10^9/L$) Grade 2 (ANC < $1.5 - 1.0 \times 10^9/L$)	Maintain dose level
Grade 3 (ANC < $1.0 - 0.5 \times 10^9/L$) Grade 4 (ANC < $0.5 \times 10^9/L$)	Omit dose until resolved to \leq Grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then $\downarrow 1$ dose level
Febrile neutropenia (ANC < $1.0 \times 10^9/L$, with a single temperature of $\geq 38.3^\circ C$ or a sustained temperature of $\geq 38^\circ C$ for more than one hour)	Omit dose until resolved, then $\downarrow 1$ dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - $75 \times 10^9/L$) Grade 2 (PLT < $75 - 50 \times 10^9/L$)	Maintain dose level
Grade 3 (PLT < $50 - 25 \times 10^9/L$)	Omit dose until resolved to \leq Grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then $\downarrow 1$ dose level
Grade 4 (PLT < $25 \times 10^9/L$)	Omit dose until resolved to \leq Grade 1, then $\downarrow 1$ dose level
RENAL	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to \leq grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then $\downarrow 1$ dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from BKM120
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from BKM120
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	
Grade 1 (> ULN - $1.5 \times ULN$)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> $1.5 - 3.0 \times ULN$) with ALT or AST $\leq 3.0 \times ULN$	Omit dose until resolved to \leq Grade 1, then: -- If resolved in ≤ 7 days, then maintain dose level -- If resolved in > 7 days, then $\downarrow 1$ dose level
Grade 3 (> $3.0 - 10.0 \times ULN$) with ALT or AST $\leq 3.0 \times ULN$	Omit dose until resolved to \leq Grade 1, then: -- If resolved in ≤ 7 days, $\downarrow 1$ dose level -- If resolved in > 7 days discontinue patient from BKM120
Grade 4 (> $10.0 \times ULN$)	Permanently discontinue patient from BKM120

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
AST or ALT	
AST or ALT without bilirubin elevation > 2ULN Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Same grade as baseline (i.e. Grade 0 or Grade 1 (> ULN – 3.0 x ULN) if presence of liver metastasis)	Maintain dose level with LFTs* monitored per protocol
Increase from baseline Grade 0 to > 1.5 ULN or from baseline Grade 1 to Grade 2	Can continue treatment at ↓ 1 dose level
Increase of two grades from baseline (from baseline Grade 0 to Grade 2 or from baseline Grade 1 to Grade 3)	Omit dose until resolved to Grade 1 or less, then ↓ 1 dose level** If no recovery in ≤ 28 days, discontinue permanently BKM120
Grade 4 (> 20.0 x ULN)	Discontinue BKM120 permanently
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue BKM120
<p>*(LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT)</p> <p>** In case of recurring Grade 3 or higher toxicity after re-challenge, patients should be permanently discontinued</p> <p>*** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis must immediately be withdrawn from BKM120 and every attempt should be made to carry out the liver event follow-up assessments as described below in Section 6.3.2.2 and Section 7.2.2.5.8.</p> <p>Hepatic toxicity monitoring (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT):</p> <p>- Cycle 1 and 2: every other week (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT, or bilirubin* values</p> <p>- Cycle 3 and onward: monthly or more frequently if clinically indicated</p> <p>In case of any occurrence of ALT/AST, or bilirubin* increase ≥ grade 2 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1</p> <p>In case of any occurrence of ALT/ AST or bilirubin* increase ≥ grade 3 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication</p> <p>Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).</p>	

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
ENDOCRINE/METABOLIC	
Fasting Plasma Glucose (FPG)	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]	<p>Maintain dose level, check FPG every week</p> <ul style="list-style-type: none"> - initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion - instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study - consider use of oral anti-hyperglycemic therapy such as metformin (or intensify existing medications) -check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	<ul style="list-style-type: none"> - If signs or symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), omit BKM120 immediately and manage as for Grade 3 hyperglycemia (below) - If asymptomatic, maintain dose and re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 2: <ul style="list-style-type: none"> -- maintain dose level and monitor FPG at least weekly until FPG resolves to ≤ Grade 1 -- initiate or intensify medication with appropriate anti-diabetic treatment such as metformin; consider adding a second oral agent if no improvement after several days. --- instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study - If FPG does not resolve to ≤ Grade 1 within 14 days after initiation/intensifying of appropriate anti-diabetic treatment, reduce BKM120 by 1 dose level -Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	<ul style="list-style-type: none"> - Immediately omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check FPG within 24 hours. If grade worsens or improves then follow specific grade recommendations. If FPG remains at Grade 3: <ul style="list-style-type: none"> -- administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate -- continue to omit BKM120 -- monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 -- If FPG resolves to ≤ Grade 1 in 7 days or less, then re-start BKM120 and ↓ 1 dose level -- If FPG remains greater than Grade 1 severity for more than 7 days, then discontinue patient from BKM120

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
	<p>-- initiate or continue anti-diabetic treatment as appropriate</p> <p>--- instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study</p> <p>--- consider use of oral anti-hyperglycemic therapy such as metformin</p> <p>-- check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks</p> <p>For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit BKM120 and following guidance for management of Grade 3 fasting plasma glucose (FPG)</p>
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	<p>- immediately omit BKM120, initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4:</p> <p>-- administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate</p> <p>-- discontinue patient from BKM120</p> <p>-- instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study</p> <p>-- consider use of oral anti-hyperglycemic therapy such as metformin</p> <p>-- check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated</p> <p>For non-fasting plasma glucose >500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue BKM120 and following guidance for management of Grade 4 fasting plasma glucose (FPG).</p>
CARDIAC	
Cardiac - Left Ventricular systolic dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue BKM120 with caution Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	<p>- Omit BKM120 until resolved* (as defined below), then ↓ 1 dose level</p> <p>- LVEF measurement to be repeated, if not resolved* within 28 days, permanently discontinue patient from BKM120 treatment</p>
Refractory or poorly controlled, ejection fraction < 20%	- Permanently discontinue patient from BKM120
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.	

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	<p>First Occurrence:</p> <ul style="list-style-type: none"> - omit BKM120 - Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. - Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline - If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. - Once QTcF prolongation has resolved, BKM120 may be restarted at a one lower dose level <p>Second Occurrence:</p> <ul style="list-style-type: none"> - Permanently discontinue patient from BKM120
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from BKM120
OTHER	
Mood alteration	
* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.	
Grade 1*	<ul style="list-style-type: none"> • Maintain dose level <p>Consider psychiatric consultation at the investigator's discretion and introduce appropriate psychotropic management except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide optimal management</p>
Grade 2*	<ul style="list-style-type: none"> • Omit dose until resolved to ≤ Grade 1 or baseline status • Consider psychiatric consultation at the investigator's discretion and introduce appropriate optimal psychotropic management except in presence of suicidal ideation where dose must be interrupted and psychiatric consultation is required to provide optimal management • First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue psychotropic treatment and reinitiate study drug at the same dose level • Second and further events: if the condition resolved to Grade ≤ 1 or to baseline status, continue psychotropic treatment and reinitiate study drug ↓ 1 dose level
Grade 3*	<ul style="list-style-type: none"> • Omit dose until resolved to ≤ Grade 1 or baseline status • Psychiatric consultation is required <p>Introduce appropriate psychotropic management</p> <ul style="list-style-type: none"> • If the condition resolved to Grade ≤ 1 or to baseline status, continue psychotropic treatment and reinitiate study drug ↓ 1 dose level

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
Grade 4*	<ul style="list-style-type: none"> Permanently discontinue patient from BKM120 Psychiatric consultation is required. Introduce appropriate psychotropic management
<p>* A timely interview with the patient after the questionnaire completion is recommended. For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3") and/or the patient presents with suicidal ideation, interrupt study drug and refer patient for psychiatric consultation regardless of the total questionnaire score or CTCAE grading for optimal management and to confirm if study drug should be interrupted or permanently discontinued. If the patient does not respond to question 9 on the PHQ-9 or to the whole questionnaire, then the investigator must assess if the patient has suicidal ideation. If the investigator identifies suicidal ideation, then study drug must be interrupted and the patient referred for psychiatric consultation for assessment.</p>	
Rash	
Grade 1	Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 2	First occurrence: Omit dose until resolved to grade ≤ 1 then: <ul style="list-style-type: none"> If resolved in ≤ 2 weeks, maintain dose level. If resolved in more than 2 weeks, $\downarrow 1$ dose level. Second occurrence: $\downarrow 1$ dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 3	First occurrence: Omit dose until resolved to CTCAE Grade \leq Grade 1, then re-start at \downarrow dose level. Second occurrence: permanently discontinue patient from BKM120/placebo. If skin rash is readily manageable, re-introduction at a reduced dose level might be considered at the discretion of the investigator. According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.
Grade 4	Permanently discontinue patient from BKM120 According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to \leq Grade 1, then: <ul style="list-style-type: none"> - If resolved in ≤ 7 days, maintain dose level - If resolved in > 7 days, $\downarrow 1$ dose level
Grade 4	Permanently discontinue patient from BKM120
Pneumonitis	please see Section 6.3.2.1.2
Other non- hematological adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to \leq Grade 1, then $\downarrow 1$ dose level
Grade 4	Permanently discontinue patient from BKM120 Note: Omit dose for \geq Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic

Dose Modifications for BKM120	
Worst toxicity (CTCAE 4.03 Grade)**	Dose Modifications for BKM120
Stomatitis/Oral mucositis	
Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash (see also Section 6.3.2.1.3)
Intolerable Grade 2 or Grade 3	First occurrence: hold until resolved to grade \leq G1 and \downarrow 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until resolved to grade \leq G1 and \downarrow 1 dose level.
Grade 4	Permanently discontinue patient from BKM120
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	

6.3.2.1.1 Additional follow-up for selected toxicities

6.3.2.1.2 Management of Pneumonitis in patients receiving BKM120

All patients participating in clinical trials with BKM120 will be routinely asked about and observed for the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function tests should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed Pneumonitis. In case of a documented Pneumonitis, the guidelines (including dose modifications) in [Table 6-4](#) should be followed. Consultation with a pulmonologist is highly recommended for any Pneumonitis case during the study treatment.

Table 6-4 Management of Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	BKM120 Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of BKM120 dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce BKM120 dose by 1 dose level (see Table 6-3) until recovery to < Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to < Grade 1 within 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with BKM120 until recovery to < Grade 1. May restart study treatment within 28 days at a reduced dose (by one level) if evidence of clinical benefit.

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	BKM120 Dose Adjustment
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with BKM120.

6.3.2.1.3 Guidelines for the treatment of study drug induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention. Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/ oral mucositis and instructed to report promptly any signs or symptoms to their physician,

Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with BKM120 metabolism (see [Section 6.3](#)).

6.3.2.1.4 Guidelines for the treatment of study drug induced diarrhea

The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity).

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Concomitant medication for the treatment of diarrhea should be considered, as per local practice and best investigator's judgment and may consist for example, as per "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" ([Benson et al 2004](#)), of loperamide given at a standard dose (e.g. initial administration of 4mg, then 2mg every 4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures could be considered for grade 1-2 diarrhea. More severe diarrhea should be treated appropriately according to investigator discretion, including for example IV fluids.

Dose adaptations of BKM120 in case of treatment related diarrhea should follow the guidelines presented above for other non-hematological adverse events.

6.3.2.1.5 Guidelines for the treatment of study drug induced psychiatric disorders

Psychiatric adverse events will be closely monitored and evaluated at each planned visit until recovery to Grade ≤ 1 or baseline status. The grading of psychiatric adverse events/mood alterations must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03) guidelines.

For patients who experience new or worsening of existing psychiatric AEs of Grade ≥ 1 , psychiatric consultation should be considered as described in [Table 6-3](#).

Patient self-reported mood questionnaires (GAD-7 and PHQ-9) will be used for screening and during the study treatment phase to aid the investigator in identifying new or worsening of events. For additional information regarding safety assessments based on patient self-reported mood questionnaires, please refer to [Section 7.2.2.8](#).

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), or patient exhibits suicidal ideation, interrupt treatment with study drug and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading and to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment.

During the study, subjects will be monitored at regular scheduled visits (eg, Day 1 of each cycle and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator if desired.

6.3.2.1.6 Guidelines for the treatment of study drug induced skin toxicity

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event.

Although preclinical experiments demonstrated that BKM120 has no potential phototoxic effect, it is recommended to caution patients to avoid sun exposure during treatment with BKM120, especially when they already have experienced rash or other skin toxicities. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the use of hats, long-sleeve shirts and long pants when outdoors.

6.3.2.2 Management of hepatotoxicity (ALT and/or AST $>3.0\times$ ULN and total bilirubin $>2.0\times$ ULN) in patients receiving BKM120

Criteria for interruption and re-initiation of BKM120 treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in [Section 6.3](#), Dose Modification ([Table 6-3](#)).

Patients with clinically significant liver test abnormalities should perform liver-directed medical history, physical examination and other tests as medically indicated to assess potential relationship with study treatment and rule out other underlying causes (e.g. disease

progression/obstruction, infection/hepatitis or other liver diseases, sepsis, metabolic diseases including diabetes, concomitant medications including herbals, alcohol, drug-drug interaction, cardiovascular disease/ischemia, other organ injuries, etc.). Any pre-existing liver conditions or risk factors should be reported in the respective medical history and concomitant medication CRF pages (if not done already).

All patients with ALT or AST $>3.0 \times$ ULN and total bilirubin $> 2.0 \times$ ULN in the absence of cholestasis (elevation of ALP in patients without bone metastasis or if bone metastasis are present elevation of 5'-nucleotidase and ALP liver fraction) must be immediately withdrawn from BKM120, and every attempt should be made to carry out locally the **liver event follow-up assessments** as described below:

- Inform the sponsor about the event immediately after its occurrence by reporting the event immediately in the clinical database if it meets the criteria for an AE or SAE.
- Evaluate if associated with the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, or other organ involvement.
- Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease including metastasis or new lesions, obstruction/compression, etc.
- Perform viral hepatitis and other serology tests:
 - Hepatitis C (HCV) serology and viral RNA, Hepatitis B (HBV) serology and viral DNA, Hepatitis A (HAV) Immunoglobulin M (IgM) and HAV total
 - Hepatitis E (HEV) serology: IgM and IgG, viral RNA
 - Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein-Barr viral (EBV) serology
- Verify and record the use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Consultation with a specialist(s) or a hepatologist(s) is recommended.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury
- LFTs should be followed-up weekly until resolve to \leq grade 1, baseline or stabilization (no CTCAE grade change over 4 weeks) and outcome documented on the respective AE and lab chemistry pages.

6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted (see [Section 6.4.1](#)), except as specifically prohibited (see [Section 6.4.2](#)).

All medications (excluding study treatment and prior antineoplastic treatments), procedures and significant non-drug therapies (including physical therapy and blood transfusions)

administered within 28 days prior to the administration of BKM120 through 30 days after the last dose of study treatment will be recorded in the Concomitant Medications/Significant Non-Drug Therapies eCRF page. Medications include not only physician prescribed medications, but also all over-the-counter medications, herbal medications (prohibited, see [Section 6.4.2.8](#)) and food or vitamin supplements. The investigator should instruct the patient to notify the investigational site about any new medications she takes after the start of the study drug.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be listed on the Concomitant Medications/Significant Non-Drug Therapies eCRF page.

6.4.1 Permitted concomitant therapy

6.4.1.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing BKM120 drug exposure to sub-therapeutic levels. Systemic corticosteroid treatment must not be given during the study, except for:

- topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- a short duration (< 5 days) of systemic corticosteroids \leq to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic);

6.4.1.2 Drugs that are metabolized by CYP450 enzymes

In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of CYP450 enzymes showed that BKM120 is a weak, reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Note that with the data available, it is not possible to confirm whether such interactions will occur in patients. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications must be monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate.

Refer to [Table 14-2](#) in [Appendix 2](#) for a list of CYP3A and CYP2C substrates to be used with caution. Particularly, caution is advised when BKM120 is co-administered with drugs that are sensitive substrates and/or have a narrow therapeutic index (e.g., SSRI).

Concomitant treatment of BKM120 with weak inducers of CYP3A4 is permitted, however, duration of concomitant treatment should be kept as short as possible (e.g., less than 1 week), or fully avoided whenever possible. Note that coadministration of BKM120 with strong and moderate inducers is prohibited (refer to [Section 6.4.2.7](#)).

6.4.1.3 Non-enzyme Inducing Anti-epileptic drugs

Non-enzyme inducing anti-epileptic medication (Non-EIAED) is allowed, except for those listed in [Table 14-1](#) in [Appendix 1](#).

6.4.1.4 Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease. No dose modification of study treatment is needed during radiotherapy.

6.4.1.5 Drugs with a conditional or possible risk to induce Torsades de Pointes

If a patient, after enrollment in the study, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for Torsades de Pointes included in [Table 14-4](#) of [Appendix 4](#), then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be closely monitored.

6.4.1.6 Gastric protection agents

BKM120 is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract may alter the solubility of BKM120 and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. BKM120 should be dosed in a staggered manner at least 1 hour before or 10 hours after dosing with medicinal products that may alter the pH of the upper GI tract.

6.4.1.7 Allopurinol and rasburicase

Allopurinol or rasburicase may be used at the physician's discretion in DLBCL patients at risk for tumor lysis syndrome.

6.4.2 Prohibited concomitant therapy

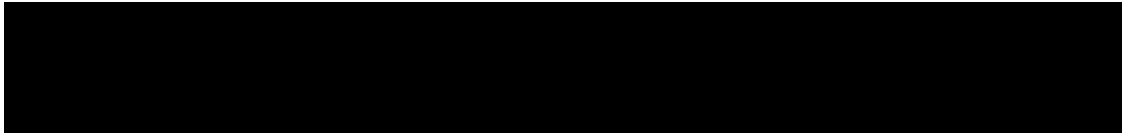
Prohibited concomitant therapy should be stopped at least 5 half-lives or 7 days whichever is the longest before start of study treatment (C1D1) and must not be used while the patient is on study.

6.4.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is enrolled in the treatment portion of the trial. If such agents are required for a patient then the patient must be permanently discontinued from the treatment portion of the study.

6.4.2.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.



6.4.2.3 Hematopoietic growth factors

Prophylactic use of hematopoietic growth factors (e.g. erythropoietins, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF)) are not permitted. However, in the event of an emergency (e.g. acute myelosuppression with infection), a patient may be given hematopoietic growth factors according to the investigator's judgment, and the sponsor should be notified as soon as possible. Subsequent secondary prevention use is permitted at investigator's discretion.

Patients who begin erythropoietin or darbepoetin therapy before randomization, may continue this treatment at the discretion of the investigator.

6.4.2.4 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulants are not permitted.

BKM120 is a weak inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Despite the fact that the inhibitory signal was weak, an increase of 40-50% of warfarin exposure is possible and for a drug like warfarin, this might be clinically relevant.

6.4.2.5 Enzyme-inducing anti-epileptic drug (EIAED)

Use of enzyme-inducing anti-epileptic drug (EIAED) is not permitted. Refer to [Table 14-1](#) for a list of prohibited EIAED.

If a patient is currently taking EIAED, they must have discontinued the EIAED therapy for at least two weeks prior to starting study drug.

If a patient is previously on a non-EIAED and needs to permanently change the anticonvulsant agent, but cannot change to another non-EIAED, the patient will be taken off BKM120.

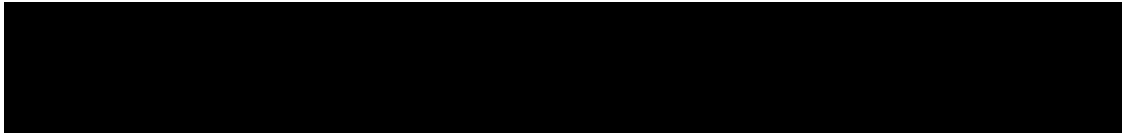
6.4.2.6 Drugs with a known risk for Torsades de Pointes

If a patient requires the concomitant use of any medication included in [Table 14-3](#) in [Appendix 3](#) entitled "List of Prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a risk of causing Torsade de Pointes), study treatment must be delayed. Note that Table 14-3 lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP. Study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.

Please also refer to <http://crediblemeds.org/> for a comprehensive list of agents that prolong the QT interval.

6.4.2.7 Moderate and strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of BKM120 is predominantly mediated by CYP3A4 and UGT1A4. Coadministration of BKM120 with strong and moderate CYP3A4 inhibitors and inducers is predicted to respectively increase or decrease the systemic exposure to BKM120.



Please refer to [Table 14-1](#) in [Appendix 1](#) for a list of prohibited drugs. Please note that this list may not be comprehensive.

6.4.2.8 Herbal medications

Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.

6.4.2.9 Hormonal contraception

Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving BKM120.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available at the site.

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

Re-screening is permitted for patients as long as all screening procedures are performed within the specific time window. Any re-screened patient must retain the same Subject No. Re-screening of patients is only allowed once per patient.

If the patient fails to be assigned to treatment for any reason, the reason will be entered into the Screening log eCRF page.

6.5.2 Treatment assignment or randomization

Not applicable.

6.5.3 Treatment blinding

This is an open-label study.



6.6 Study drug supply

6.6.1 Study drug preparation and dispensation

Study medication will be dispensed by an authorized person at the investigator's site. Investigator staff will add the patient number on the label. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive BKM120 on an outpatient basis. The investigator shall provide the patient with instructions for BKM120 administration according to the protocol.

All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.2 Study drug packaging and labeling

BKM120 will be supplied as 10 mg and 50 mg hard gelatin capsules, packaged in bottles, and will be given orally on a flat scale of mg/day. The capsules are packaged in HDPE bottles with a plastic child resistant closure.

Medication labels will comply with the legal requirements of each country and printed in the local language for each specific country. The storage conditions for study drug will be described on the medication label.

Immediately before dispensing the study drug to the patient, the investigator or his/her designee will detach the outer part of the label from the packaging and affix it to the source document containing that patient's unique patient number.

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
BKM120	Capsules in bottle 10 mg 50 mg	Labeled as "BKM120" Once daily dosing

6.6.3 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure]. These instructions should also be made clear to the patient for storage and self-administration of BKM120 at home.

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

Compliance will be assessed and verified by the investigator and/or study personnel at each patient visit by counting the number of BKM120 capsules consumed between visits and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Any overdose must be recorded in the dosage administration record of the eCRF. An overdose is defined as any dose greater than the daily dose level at which the patient is being treated. If the subject has taken a higher dose than stated in the protocol, then the patient should also be monitored for potential adverse reactions. In case of an overdose that needs to be treated, the investigator should use his or her clinical judgment for the management of this overdose and apply adequate supportive care and follow up until recovery.

6.6.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

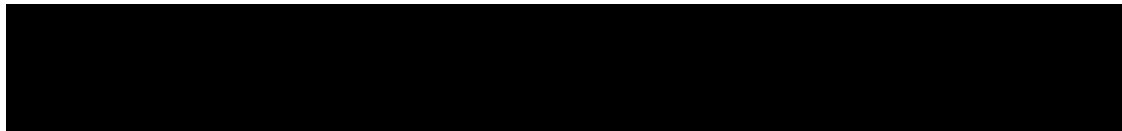
At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4.3 Handling of other study treatment

Not applicable.

6.6.5 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.



7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) (“Category” column).

All visits can take place 3 days before or 3 days after the specified study visit (total window of 7 days) except for the time window for the end of treatment and safety follow-up visit which is +7 days.

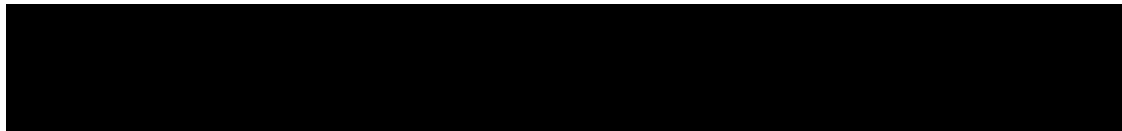


Table 7-1 Visit evaluation schedule

	Category	Reference to Section	Screening	Cycle 1 (28 days)	Cycle 1	Cycle 1	Cycle 1	Cycle 2 (28 days)	Cycle 3 (28 days)	Subsequent cycles (28 days)	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up (FU)	Completion of Study (end of Efficacy FU)	Overall Survival follow-up
Visit Number			1	2	601	602	603	3	4	5	777	501		778	
Day of cycle			-28 to -1	1	2	3	4	1	1	1		EOT + 30 (+7) days			
Obtain Informed Consent	D	4.1 & 11.3	X												
Patient history															
Demography	D	7.1.2.3	X												
Inclusion/exclusion criteria	D	5.2 & 5.3	X												
Relevant medical history/current medical conditions	D	7.1.2.3	X												
Diagnosis and extent of cancer	D	7.1.2.3	X												
Prior antineoplastic therapy	D	7.1.2.3	X												
Prior/concomitant medications	D	7.1.2.3 & 6.4	X	Continuous											
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5 & 7.1.6.3									X	X		X	X

[illegible]

[illegible]

	Category	Reference to Section	Screening	Cycle 1 (28 days)	Cycle 1	Cycle 1	Cycle 1	Cycle 2 (28 days)	Cycle 3 (28 days)	Subsequent cycles (28 days)	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up (FU)	Completion of Study (end of Efficacy FU)	Overall Survival follow-up	
Visit Number			1	2	601	602	603	3	4	5	777	501		778		
Day of cycle			-28 to -1	1	2	3	4	1	1	1		EOT + 30 (+7) days				
Safety																
Adverse events	D	7.2.2	X	Continuous												
[REDACTED]																
BKM120 kit dispensation	S	6.6.1		X				X	X	X						
Drug administration	D	6.1.1.1		Continuous												
Screening Log	D	7.1.2	X													
End of Treatment	D	7.1.5									X					

[REDACTED]

[illegible]

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

After signing the main study ICF (S-ICF) for the study, the remaining screening assessments will be done generally within 7 to 28 days prior to start of treatment (see [Table 7-1](#)).

Please note that the screening period must not exceed 28 days.

7.1.2.1 Eligibility screening

Following registration for screening, patient eligibility will be checked once all screening procedures are completed. The investigator will complete the Screening Log and Inclusion/Exclusion criteria eCRF pages.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log eCRF Page. The following CRFs must be completed for screen failure patients:

- Screening failure log (including reason for not being started on treatment)
- Demography

7.1.2.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, gender, race) and other background or relevant medical history, including history of disease and current disease status, staging ([Table 7-2](#)), bone marrow involvement, sites of disease, prior anticancer therapies, prior medications/significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study (i.e., ECOG Performance Status, complete physical examination (including neurological assessment, tumor assessment and B symptoms [Table 7-2](#)), vital signs, hematology, blood chemistries including coagulation studies and a serum lipid profile, pregnancy test only required for women of childbearing potential, 12-lead ECG). Furthermore the following assessments will be performed to assess the eligibility of the patient:

- Viral hepatitis serology [e.g. HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb] and other tests (see [Section 6.3.2.2](#) and [Section 7.2.2.5.8](#))

Table 7-2 Ann Arbor staging classification¹

Stage Area of involvement

I Single lymph node group
II Multiple lymph node groups on the same side of the diaphragm
III Multiple lymph node groups on both sides of the diaphragm
IV Multiple extranodal sites or lymph nodes and extranodal disease
X Bulk disease > 10 cm
E Extranodal extension or single isolated site of extranodal disease
Class A patients who experience no B symptoms
Class B patients experience unexplained fever of $\geq 38^{\circ}\text{C}$; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months

¹ Cotswolds modification of Ann Arbor staging system adapted from 2007 NCCI guidelines for non-Hodgkin's lymphoma

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

Patients will receive study treatment BKM120 daily as a 28 day cycle until disease progression, unacceptable toxicity or until other discontinuation criteria are met, whichever come first.

Following initiation of study treatment (Cycle 1 Day 1), the patient should visit the site every cycle; see [Table 7-1](#). Permitted visit windows for assessments within the treatment period and at efficacy follow-up visits: +/- 3 days of the protocol required date.

Information on drug exposure will be collected on the Dosage Administration Record eCRF. Concomitant medications/significant non-drug therapies prior to start (≤ 28 days) and after start of study treatment will be recorded on the appropriate eCRFs.

Compliance will be assessed by the investigator and/or study personnel at each visit using box counts and information provided by the caregiver. This information should be captured in the source document at each visit (Please also refer to [Section 6.6.4](#)).

7.1.5 End of treatment visit including study completion and premature withdrawal

Patients will continue study treatment until disease progression or until any of the study's discontinuation criteria ([Section 7.1.5.1](#)) are met.

Patients who discontinue study treatment should be scheduled for an End-of-Treatment visit as early as for patient's convenience, but it should occur within 7 days from treatment discontinuation, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to [Table 7-1](#).

An End of Treatment eCRF page should be completed, giving the date and reason for discontinuation of study treatment.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF page.

Patients who discontinue study treatment for reasons other than disease progression will enter the efficacy follow-up period until disease progression or initiation of a new antineoplastic therapy and should not be considered withdrawn from the study.

7.1.5.1 Criteria for premature patient withdrawal

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Unacceptable toxicities
- Protocol deviation
- Lost to follow-up
- Pregnancy
- Discovery of patient ineligibility
- Errors in treatment compliance
- Administrative problems
- Death

In addition to the general study treatment withdrawal criteria, the following **study specific criteria** will also require premature study treatment discontinuation:

- Study treatment modifications that result in discontinuation.
- Interruption of BKM120 treatment for more than 28 days
- Use of prohibited medication.
- Start of any other anti-neoplastic therapy

If a study treatment withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from study treatment and record this information on the End of Treatment CRF page. In case of withdrawal from study treatment, the patient needs to indicate on the informed consent form whether she is willing to continue with subsequent follow-up procedures.

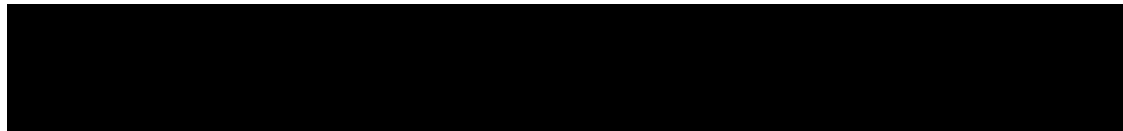
7.1.5.2 Replacement policy

Not applicable.

7.1.6 Follow up period

All patients must be followed for safety for at least 30 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source



documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.1.6.1 Safety follow up

All patients will be followed for adverse events and serious adverse events for at least 30 days following the last dose of BKM120. At the end of this period (between day 30 and day 37 after last dose), the investigator should contact the patient to inquire about any AE observed/concomitant medication taken during this period. This could be done via either an office visit or a phone contact.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first. In case the patient has any abnormal lab values at end of treatment that are considered clinically significant by the investigator, the patient needs to come to the site for repeat blood analysis until resolution or stabilization including at least a site visit with respective analyses 30-37 days after end of treatment.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

All new anti-cancer therapies given after the last dose of the study drug will be recorded on eCRFs designed to capture anti-neoplastic therapies administered after discontinuation of study treatment.

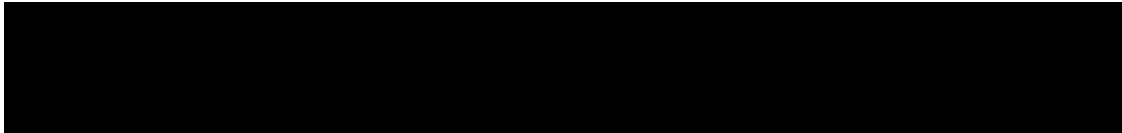
7.1.6.2 Efficacy follow up

Patients who discontinue study treatment for reasons other than disease progression, death start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up will continue to have radiological tumor assessments every 8 weeks (\pm 7 days) until 6 months after last patient in the same cohort has started the study treatment, or until disease progression, start of a new antineoplastic therapy, death, lost to follow-up, withdrawn consent to efficacy follow-up, whichever comes first.

At the time the patient discontinues the efficacy follow-up period, the Study Evaluation Completion page should be completed. In case the patient starts a new antineoplastic therapy, this will be recorded on the Antineoplastic therapies since discontinuation of study treatment CRF page.

7.1.6.3 Survival follow up

All patients who discontinue study treatment and are no longer followed radiologically will be contacted for survival information every 12 weeks (\pm 7 days) from the time of the End of Treatment (EoT) visit or, where applicable, from the last visit in the efficacy follow-up period until death. Further, patients who refuse to return for scheduled visits or are unable to do so should be asked to consent for survival follow-up. If applicable, the date of death should be captured on the End of Treatment page, Study Evaluation Completion, or Survival Follow Up (whichever is applicable) page in the eCRF.



The survival follow-up period will continue for 6 months after the last patient in the same cohort has started the study treatment, or until all patients in the same cohort have discontinued efficacy follow up, whichever comes first.

7.2 Assessment types

7.2.1 Efficacy assessments

The primary efficacy endpoint is the overall response rate, as defined in [Section 10.4.1](#). Secondary efficacy endpoints are duration of response, progression-free survival and overall survival as defined in [Section 10.5.2](#).

Response will be evaluated, using modified criteria for malignant lymphoma (adapted from [Cheson et al 1999](#) and [Cheson et al 2007](#)). PET scan will not be used in this study, as it is not yet widely accepted by clinicians and regulatory agencies for assessing response to treatment of NHLs, and it may not be available in all of the participating centers. Otherwise, response criteria will generally follow the CT scan recommendations in the later publication ([Cheson et al 2007](#)). Further clarification on these criteria has been published by ([Cheson 2007b](#)). MRI will be allowed only in those cases when CT scan cannot be performed. For complete details, refer to [Appendix 5](#).

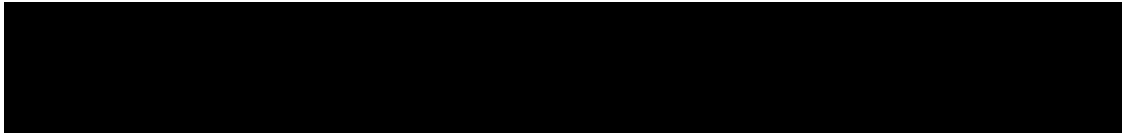
Clinical evaluation and tumor assessments will be performed periodically, as is indicated in [Table 7-1](#), based on physical examination, radiological evaluation and core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment). Tumor assessments will be performed every 2 cycles (every 8 weeks ± 7 days). Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline.

7.2.1.1 Physical examination

Tumor assessment by physical examination and evaluation of disease related B symptoms (unexplained fever of $\geq 38^{\circ}\text{C}$; unexplained, recurrent drenching night sweats; or unexplained loss of $>10\%$ body weight within the previous 6 months) will be performed and recorded following the schedule for radiological tumor assessments.

7.2.1.2 Radiological tumor assessment

At screening, all patients must have a CT scan with contrast of the Chest/Abdomen and Pelvis. The same type of CT scan used at screening must be used for all subsequent assessments. MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change would be allowed during the study. Only in exceptional cases when during the study a patient develops intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 7 days prior to the first dose of BKM120, however tumor assessments ≤ 28 days prior to first dose of study drug will be acceptable.



CT Scans of the Chest/Abdomen and Pelvis will be performed following completion of every 2 cycles. It may also be performed as clinically indicated. For visit schedule refer to [Table 7-1](#). Any patient who has been discontinued from treatment with BKM120 for any reason other than death or loss to follow-up (i.e., documented disease progression by the investigator, an AE or SAE, administrative reason, withdrawal of consent from treatment, etc.) will continue to have tumor assessments as per their current schedule until the initiation of a new anticancer therapy. The response CRFs are expected to continue being completed in a timely fashion. The investigator or his/her designee will collect information on a new anticancer therapy, given after the last dose of study drug, and record the information on the appropriate eCRF. All patients should have at least one site of measurable nodal disease > 2.0 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan cannot be performed). Complete guidance for selecting index lesions is provided in [Appendix 5](#). Index lesions will be measured and recorded at baseline and during the course of the study. They should be selected on the basis of their size and suitability for accurate repeat measurements. Skin lesions, if the area is ≥ 2 cm in at least one diameter, must be histologically conformed for lymphoma involvement (the site must document the histological confirmation (yes or no) to the corresponding CRF) and photographed (color photography using digital camera) (optional).

A sum of the product of diameters (SPD) for lesions measured prior to study treatment will be calculated and reported at baseline.

Conventional CT and MRI should be performed with contiguous cuts of 7.5 mm or less in slice thickness. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm (this specification applies to tumors of the chest, abdomen and pelvis).

If a very small lesion can not be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Any measurable extranodal lesions (organs other than lymph nodes) that resolves from baseline (disappear completely) must be assigned a size of 0 mm when documenting on the corresponding eCRFs. An extranodal lesion must be ≥ 1 cm x 1 cm to be considered measurable. Refer to [Appendix 5](#) for complete reporting guidelines.

7.2.1.3 Bone marrow assessment

Information on the patient bone marrow involvement prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered on the corresponding eCRF.

Core bone marrow biopsy is required to confirm Complete Responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a

goal of > 20 mm unilateral core). Bone marrow biopsy should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days \pm 7 days from the date of the radiological assessment, on which the CR is based on).

7.2.2 Safety and tolerability assessments

Safety assessments will be monitored by assessing all adverse events, concomitant medications, and the regular monitoring of laboratory tests (including glucose monitoring), physical examinations, weight, vital signs, as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to [Section 8](#).

7.2.2.1 Physical examination

The clinical examination comprises a total body examination that should include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, and extremities, vascular and neurological. If indicated; rectal, external genitalia, breast and pelvis exams will be performed.

Clinical examinations will be performed on the scheduled day, even if study medication is being withheld. More frequent examinations may be performed at the investigator's discretion and/or if medically indicated.

Evaluation of ocular signs and symptoms is recommended as part of the physical examination throughout the study. In case a patient develops symptoms such as tearing, ocular redness, pain, photophobia or altered vision, the possibility of a drug-induced effect should be considered. To ensure appropriate diagnosis and management, and to avoid potential complications, referral to an ophthalmologist may be required.

Information about the physical examination must be present in the source documentation at the study site. Significant findings those were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs assessments include body temperature, sitting blood pressure, and sitting pulse. Vital signs should be assessed on the scheduled day even if study treatment is being withheld. More frequent examinations may be performed at the investigator's discretion, if medically indicated. If the vital signs are determined during screening \leq 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1.

7.2.2.3 Height and weight

Weight will be performed at screening, on Day 1 Cycle 1, on Day 1 of every subsequent treatment Cycle, as clinically indicated and at the End of treatment. Height will be measured and recorded at screening only. If weight is determined during screening \leq 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1.

7.2.2.4 Performance status

The baseline ECOG performance status will be assessed and recorded at screening, on Day 1 Cycle 1, on Day 1 of every subsequent treatment Cycle, and at the End of Treatment. If the ECOG performance status is determined during screening ≤ 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1.

The ECOG scale and criteria allows patients to be classified, based on evaluation of patient's disease progression, how the disease affects the daily living abilities of the patient, and allows the determination of appropriate treatment and prognosis. The definition of scores in relation to the performance status is given in [Table 7-3](#).

Table 7-3 ECOG performance scale

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, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

As published by ([Oken et al 1982](#)). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

7.2.2.5 Laboratory evaluations

The standard clinical laboratory analyses described below are to be performed by the study site's local laboratories according to the Visit Schedule, outlined in [Table 7-1](#). Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept apprised of any updates on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance. At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the Adverse events CRF.

Laboratory data will be summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Local laboratory tests will be collected and analyzed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion if medically indicated; those results should be recorded on the Unscheduled Visit CRF.

Laboratory assessments performed as part of the screening evaluations and within 7 days of the first dose of study drug, will not be required to be repeated on Day1 of Cycle 1.

In the event of grade 2, grade 3 or grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological tests must be repeated until recovery to the baseline value or grade 1.

Hepatotoxicity follow-up testing will be performed when needed (refer to [Section 6.3.2.2](#)).

Table 7-4 Clinical laboratory parameters collection plan

Test Category	Test Name
*Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up *	HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia), and others.
* Hepatotoxicity follow-up testing/procedures will be performed locally (refer to Section 6.3.2.2 and Section 7.2.2.5.8).	

7.2.2.5.1 Hematology

Hematology includes the following parameters: complete blood count consisting of a white blood cell (WBC) count with differential (total neutrophils [including bands], lymphocytes, monocytes, eosinophils, basophils), hemoglobin (Hgb), and platelet counts.

Hematological tests will be performed at screening, on Cycle 1 Day 1 (prior to administration of the study drug) and repeated on Day 1 of every subsequent treatment Cycle and at the End of Treatment. Hematology test may also be performed as medically necessary.

7.2.2.5.2 Clinical chemistry

Clinical chemistry includes the following parameters:

- Potassium, sodium, calcium, magnesium, chloride, inorganic phosphorus
- ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, Gamma GT
- Serum creatinine, urea or blood urea nitrogen (BUN), lipase, albumin, uric acid
- Fasting plasma glucose (fasting is defined as no caloric intake for at least 8 hrs).

Clinical chemistry will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug), repeated on Day 1 of every subsequent treatment cycle and at End of Treatment. Chemistry tests may also be performed as clinically indicated. Patients with diffuse large B-cell lymphoma will require additional evaluations of the following parameters on days 2, 3 and 4 in the first treatment cycle to monitor for TLS:

- Uric acid, potassium, sodium, calcium, inorganic phosphorus and serum creatinine

7.2.2.5.3 Coagulation

The coagulation profile includes partial thromboplastin time (PTT) and either prothrombin time (PT) or International normalized ratio (INR).

Coagulation profile will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug) and as clinically indicated.

7.2.2.5.4 Lipid panel

The patient must be fasting when blood is drawn for lipid panel. Lipid panel includes total-, LDL- and HDL-cholesterol and triglycerides.

Lipid panel will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug, on Day 1 of Cycle 3, every 2nd cycle thereafter (i.e. Day 1 of Cycle 5, Day 1 of Cycle 7, etc.) and at End of Treatment.

7.2.2.5.5 C-peptide and HbA1c

The patient must be fasting when blood is drawn for C-peptide and HbA1c analysis. Analysis should be performed prior to BKM120 administration.

C-peptide and HbA1c testing will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug), on Day 1 of Cycle 3, every 2nd cycle thereafter (i.e. Day 1 of Cycle 5, Day 1 of Cycle 7, etc.) and at End of Treatment.

7.2.2.5.6 Urinalysis

Not applicable.

7.2.2.5.7 Pregnancy and assessments of fertility

Pregnancy tests are indicated for all females of childbearing potential. Serum tests are required at screening, on Cycle 1 Day 1 (prior to administration of study drug) and repeated on Day 1 of every subsequent treatment cycle and at End of Treatment. Additional serum pregnancy tests should be performed as soon as indicated in case the patient is suspected to be pregnant.

In case of pregnancy, the patient must immediately be withdrawn from study treatment. Each pregnancy in a patient on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. See [Section 8.4](#) for detailed reporting and follow up procedures.

Note: Women are considered post-menopausal and not of child bearing potential if any of the following conditions is fulfilled:

- Prior surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago.
- Age ≥ 60
- Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy), and FSH and estradiol in the postmenopausal range (serum FSH > 40 mIU/mL and estradiol < 20 pg/mL or according to the postmenopausal range definition for the laboratory involved).

7.2.2.5.8 Viral hepatitis serology and other tests for hepatotoxicity follow-up

Viral hepatitis serologic tests are performed confirm patient's eligibility when needed per clinical judgment and specific patient's clinical circumstances.

During study treatment, viral hepatitis serologic and other tests will be performed as per the guidelines of management of hepatotoxicity (ALT or AST $>3.0\times$ ULN and total bilirubin $>2.0\times$ ULN) in patients receiving BKM120, refer to [Section 6.3.2.2](#) for details.

Viral hepatitis serology includes the following:

- Hepatitis A IgM antibody and hepatitis A serology total
- Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM) and viral DNA
- Hepatitis C serology and viral RNA
- Hepatitis D RNA (where needed)
- Hepatitis E IgM and IgG antibody and viral RNA

Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.

Additional viral serology tests may include:

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Herpes Simplex Virus

7.2.2.6 Radiological examinations

Not applicable.

7.2.2.7 Cardiac assessments

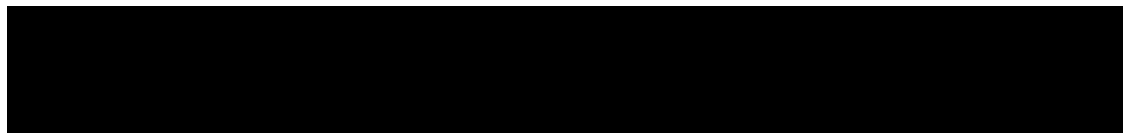
7.2.2.7.1 Electrocardiogram (ECG)

The study requires standard 12-lead digital ECG as indicated in [Table 7-1](#). Pre-dose ECGs must be performed prior to any study drug administration on the respective days.

Single ECG should generally be done prior to any blood draws.

ECGs will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug), repeated on Day 1 of every subsequent treatment cycle and at End of Treatment. ECGs may be repeated more frequently at the investigator's discretion if signs and symptoms of cardio-toxicity exist. If an ECG is performed for screening ≤ 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1.

Clinically significant findings must be discussed with the sponsor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.



7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

MUGA (multiple gated acquisitions) scan or echocardiogram (ECHO) will be used to assess LVEF at screening.

LVEF assessment may be performed as clinically indicated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported on the Adverse Events CRF.

7.2.2.8 Patient self-rating mood questionnaire

The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) will be collected to screen patients for study eligibility and to aid in the identification and severity assessment of potential mood alterations. The PHQ-9 and GAD-7 are validated ([Kroenke et al 2001](#), [Spitzer et al 2006](#), [Spitzer et al 1999](#)), patient self-administered questionnaires developed for use in clinical practices.

The GAD-7 ([Table 7-6](#)) is a one-dimensional questionnaire consisting of 7 questions. Similarly to the PHQ-9, in the GAD-7, patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the DSM IV. Response options are “not at all,” “several days,” “more than half the days,” and “nearly every day,” scored as 0, 1, 2, and 3, respectively. The sum of all seven questions calculate the total GAD-7 score. Therefore, GAD-7 scores range from 0 to 21.

The PHQ-9 ([Table 7-7](#)) consists of 9 questions that assess anhedonia, depressed mood, sleep, energy, appetite, guilt and worthlessness, concentration, feeling slowed down or restlessness, and suicidal thoughts. For each of these questions, patients are asked to rate how much over the past 2 weeks they have been bothered by the symptom. Scoring of the PHQ-9 is based on a Likert-type scale from 0 to 3 (0 indicates not at all; 1, several days; 2, more than half the days; 3, nearly every day). The sum of all nine questions is used to determine a total PHQ-9 score ranging from 0 to 27.

The patient must complete two different mood questionnaires, (PHQ-9 and GAD-7) at Screening, Cycle 1 Day 1, and Day 1 of each subsequent cycle in addition to the EOT visit. If the questionnaires are completed as part of screening ≤ 7 days before the first dose of study treatment, they do not need to be repeated on Day 1 of Cycle 1. Sites should instruct patients to complete the mood questionnaires prior to administration of any study-related treatment or clinical assessments or procedure. Additional assessments may be done according to the clinical judgment of the investigator.

All questionnaires should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. This is to avoid potentially biasing patients or their responses to study questionnaires.

Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be

made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in [Section 8](#) of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

The severity classification table described in [Table 7-5](#) for the PHQ-9 and GAD-7 will be used in this study to increase the sensitivity of identifying potential anxiety and/or depression disorders. During the study, questionnaire scores and corresponding severity classification can be used to aid the investigator in identifying new or worsening of events. Importantly, grading must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03).

Table 7-5 Classification of severity based on mood questionnaire scores

PHQ-9 (depression)		GAD-7 (anxiety)	
Score	Severity	Score	Severity
0-4	None	0-4	None
5-9	Mild	5-9	Mild
10-19	Moderate	10-14	Moderate
20-27	Severe	≥ 15	Severe

At Screening, a patient may be judged by the investigator or a psychiatrist to be ineligible based on medical mental health history as listed in the exclusion criteria. Alternatively, patients who score ≥ 12 on the PHQ-9 or ≥ 15 on the GAD-7 mood scale, respectively, or select a positive response of '1, 2, or 3' to question number 9 regarding suicidal thoughts or ideation will be excluded from the study.

A timely interview with the patient after the questionnaire completion is recommended. During the treatment phase, patients who indicate a positive response by selecting '1, 2, or 3' to question number 9 in the PHQ-9 and/or present with suicidal ideation must interrupt treatment with study drug and must be referred for psychiatric consultation for appropriate psychotropic management regardless of the total questionnaire score or CTCAE grading and to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient PHQ-9 self-assessment. If question 9 on the PHQ-9 was not answered, or the whole questionnaire was not answered, the investigator must assess the patient for suicidal ideation. If the investigator identifies suicidal ideation, then study drug must be interrupted and the patient referred for psychiatric consultation for assessment.

Investigators must not encourage the patients to change responses reported in questionnaires. Guidelines on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided with each instrument. Dosing modification guidelines

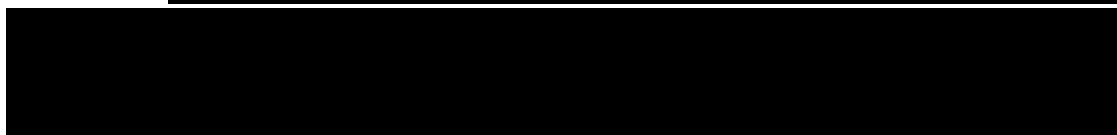
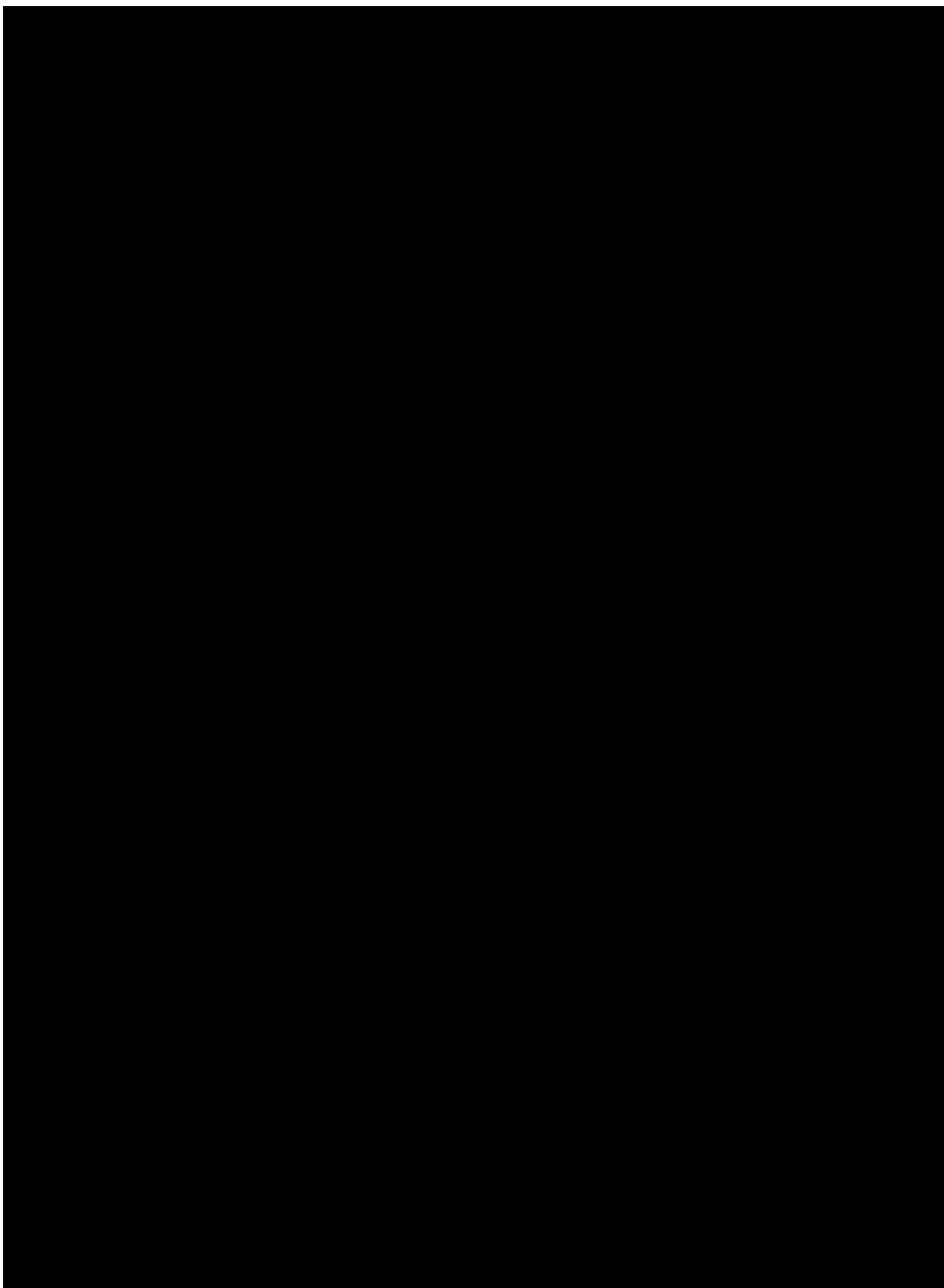
for BKM120 are provided in [Table 6-3](#). For additional information on AE reporting, please refer to [Section 8.1](#).

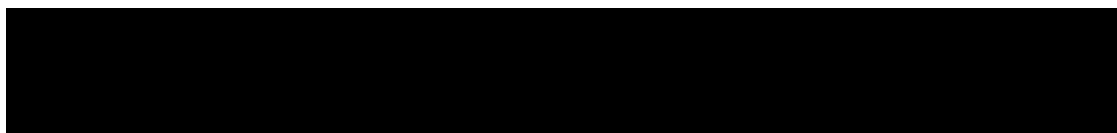
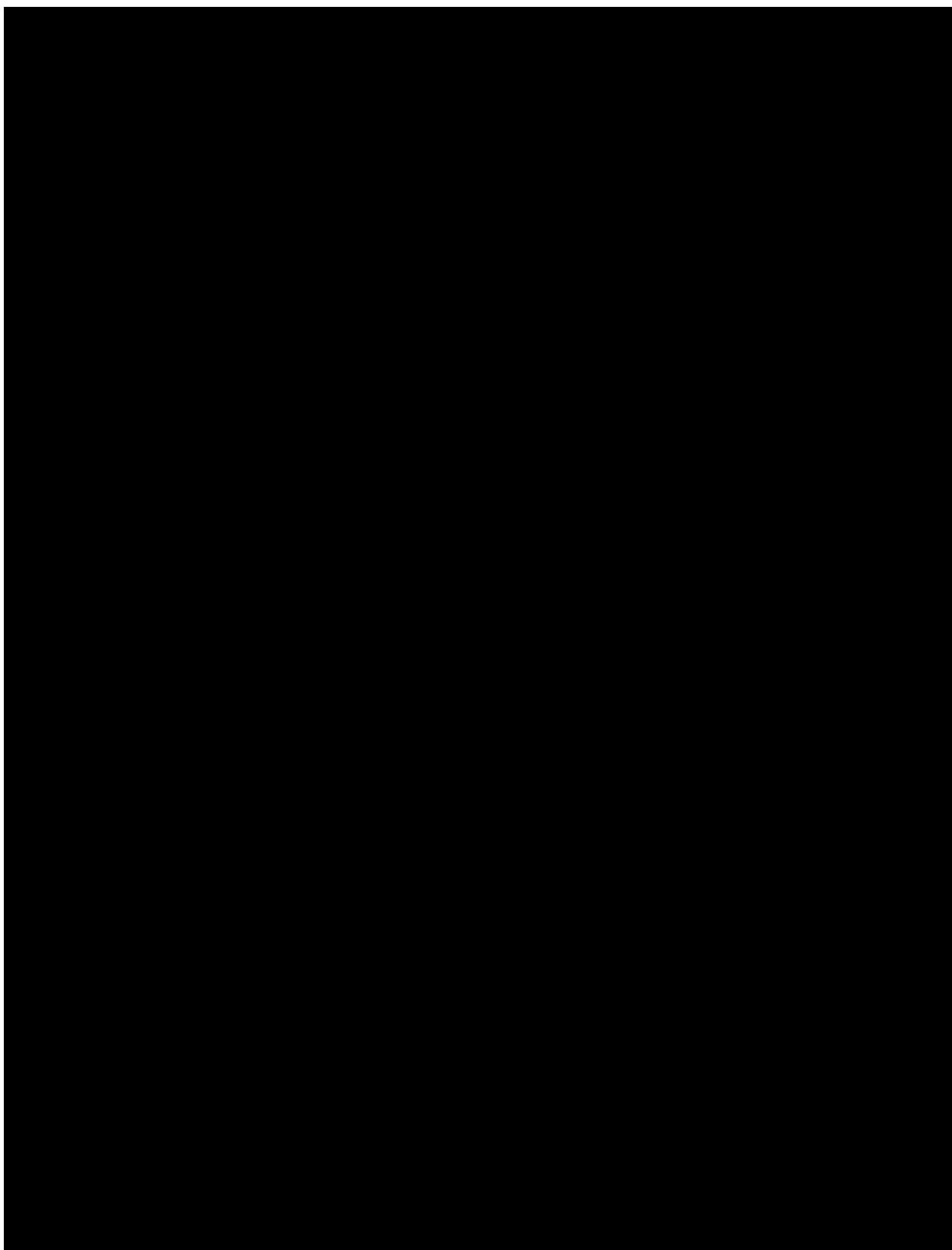
Table 7-6 GAD-7 anxiety scale

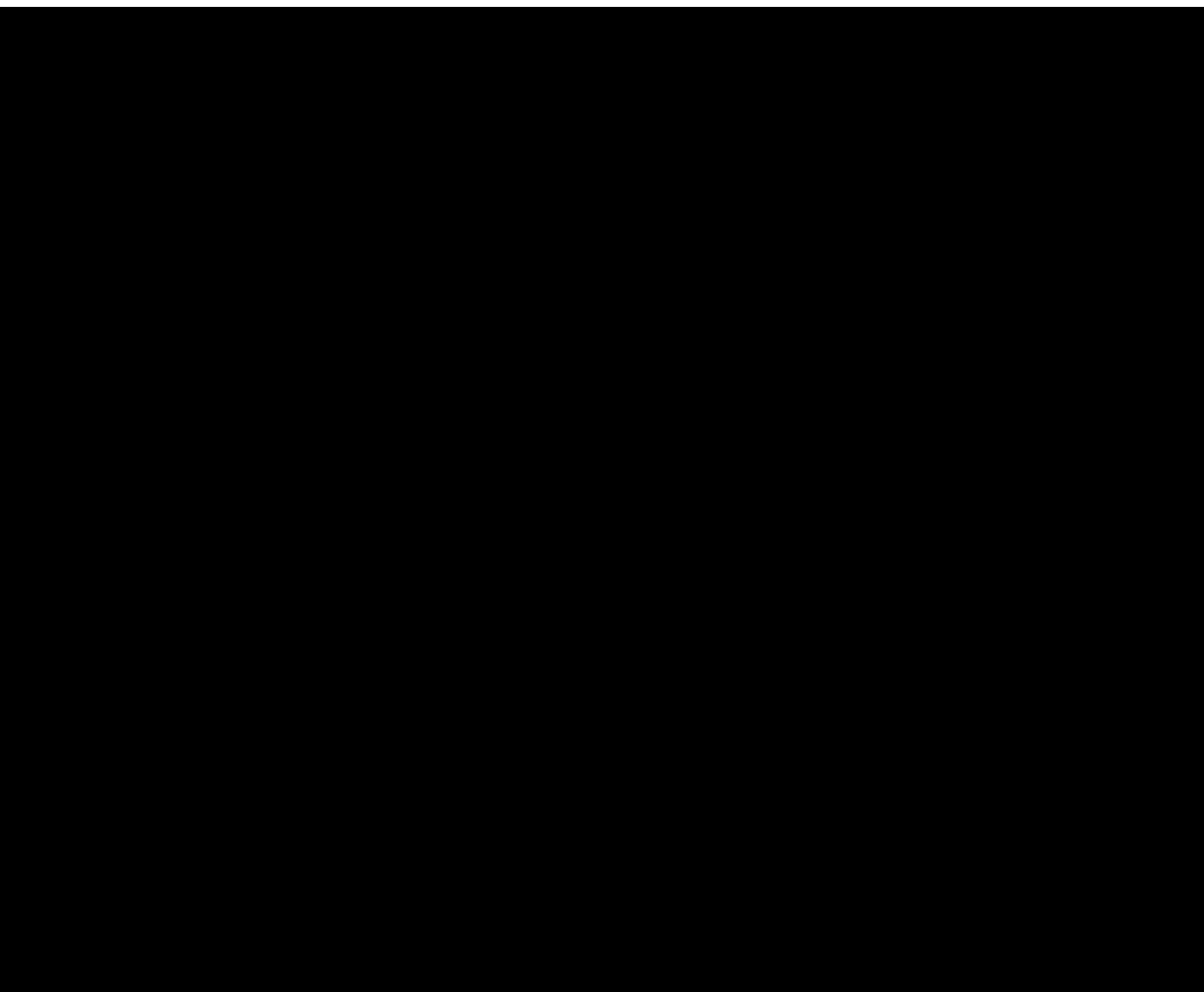
Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✓" to indicate your answer"	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Column totals:		+	+	+
= Total Score				

Table 7-7 PHQ-9 depression scale

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use “✓” to indicate your answer”	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless.	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy.	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Column totals:		+	+	+
= Total Score _____				
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?				
Not difficult at all	Somewhat difficult	Very Difficult	Extremely Difficult	







7.2.4 Other assessments

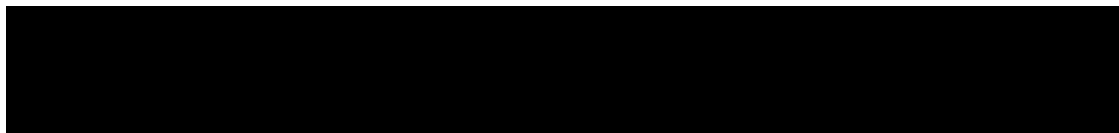
No additional tests will be performed on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).



Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected through the EOT/SEC/Survival Information eCRF pages.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
or
Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in [Section 8.2.1](#)

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Cheson criteria), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

- Serious adverse event (SAE) is defined as one of the following:
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
 - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

Protocol specific SAE: any Hy's law case of drug-induced liver toxicity should be reported as an SAE, even when assessed non-serious by the investigator. These reports will always be assessed as medically significant by Novartis in the absence of any other seriousness criteria.

- Protocol exempt SAEs: Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Cheson criteria), should not be reported as a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours Novartis.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator's Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

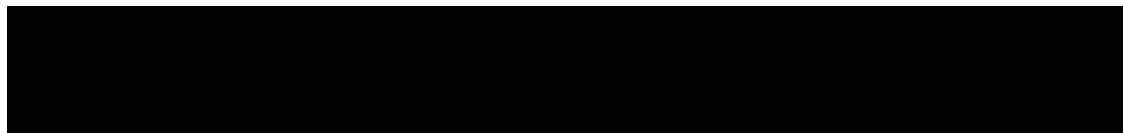
8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

The Steering Committee will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team.

The Steering Committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The Steering Committee will review protocol amendments as appropriate. Together with the clinical trial team, the Steering Committee will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.



9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

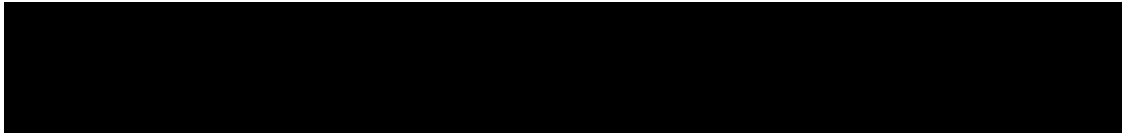
The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).



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

9.3 Data collection

This study will be using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

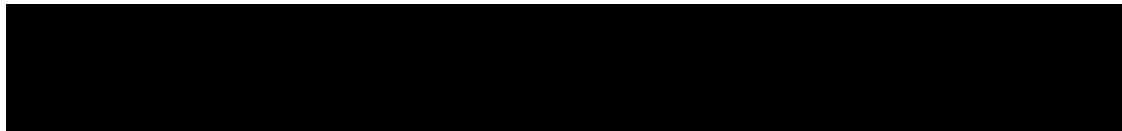
Biomarker samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The trial will include at least N = 66 subjects, i.e. N = 22 patients in each of the three histologically defined cohorts: mantle cell lymphoma, follicular lymphoma and diffuse large B-cell lymphoma. Maximum number of patients per cohort will be capped at N = 28 patients, in case of over enrollment. The final analysis for each cohort will be performed when all included patient in a cohort have finished their 6 month assessment or discontinued early.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.



If not specified otherwise, all statistical tests will use a significance level of 5% and 95% confidence intervals will be calculated.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all included patients who received at least one dose of study treatment. As a consequence, the FAS excludes screened patients who were not administered study treatment but were intended to be treated.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication and who have at least one post baseline safety assessment.

Note: The statement that a patient had no adverse events (on the Adverse Event CRF page) constitutes a safety assessment.

10.1.3 Per Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who received at least one dose of the study treatment and who have no major protocol deviations.

Oncology standards for major protocol deviations **potentially** leading to exclusion from the PPS are:

- type of indication different from those required by the clinical study protocol (CSP) (e.g. incorrect histology/cytology, not refractory, not metastatic, different grade of cancer, etc.),
- if prior therapy does not match with CSP requirements in terms of number and types of previous therapy regimens,
- missing or incomplete documentation of stage of disease (as required in the CSP),
- if ECOG performance status at least 2 categories worse than protocol-defined inclusion criteria,
- another anti-neoplastic therapy administered after start of study treatment and prior to first tumor assessment.

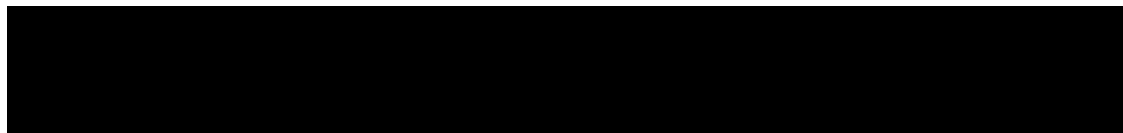
All protocol deviations leading to exclusion from the PPS will be detailed in the report and analysis plan (RAP) and validation analysis plan (VAP).

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

Not applicable.



10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by cohort for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The actual dose and duration in days of BKM120 as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics in the FAS by cohort. Dose reductions, interruptions/delays and increases (including the reasons for these) will be listed and summarized by cohort.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized for the safety set by cohort.

10.4 Primary objective

The primary objective of the trial is to determine the efficacy of BKM120 in patients with relapsed/refractory Non-Hodgkin Lymphoma in the three histological subgroups (cohorts): mantle cell lymphoma, follicular lymphoma and diffuse large B-cell lymphoma.

10.4.1 Variable

Overall response rate (ORR) is defined as the proportion of patients with a best overall response of CR or PR according to Cheson criteria ([Cheson et al 2007](#)).

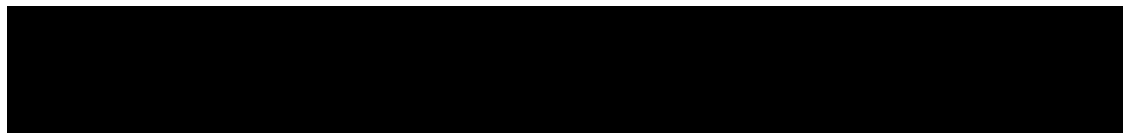
The ORR is the number of patients in a cohort who experience either complete response (CR) or partial response (PR) during their follow-up after treatment start divided by the total number of patients included in the corresponding cohort. Patients for whom the best response after treatment start is missing, 'UNK' or 'PD' will be considered as non-responders and will be counted in the denominator for the estimation of the ORR.

10.4.2 Statistical hypothesis, model, and method of analysis

The analysis for each cohort will be based on an exact binomial test comparing the ORR to the reference level of 10% (null hypothesis) in the FAS. The test for each cohort will use a significance level of 5%. The ORR will be presented together with an exact 95% Clopper-Pearson confidence interval.

10.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis of the ORR, patients without any efficacy assessment after treatment start will be counted as failures for the FAS analysis. These patients will be excluded from the PPS analysis.



10.4.4 Supportive analyses

The primary analysis will be repeated on the PPS instead of the FAS.

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of treatment start to the date of the first documented progressive disease (PD) or death due to any cause. If a patient is not known to have progressed or died at the date of the analysis cut-off of the corresponding cohort or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off date and before the anti-cancer therapy date. PFS will be based on the investigator's assessment.

PFS will be described using Kaplan-Meier curves with appropriate summary statistics.

Duration of response

Duration of response is defined as the time from the date of first occurrence of CR or PR to the date of the first documented progressive disease (PD) or death due to lymphoma. If a patient is not known to have progressed or died at the date of the analysis cut-off for the corresponding cohort, or when he/she receives any further anti-cancer therapy, duration of response is censored at the time of the last tumor assessment before the cut-off date and before the anti-cancer therapy date.

Duration of response will be described using Kaplan-Meier curves with appropriate summary statistics.

Overall survival

Overall survival (OS) is defined as the time from treatment start to the date of death due to any cause. Patients not known to have died will be censored at the date of their last available assessment or at the analysis cut-off date whichever comes earlier.

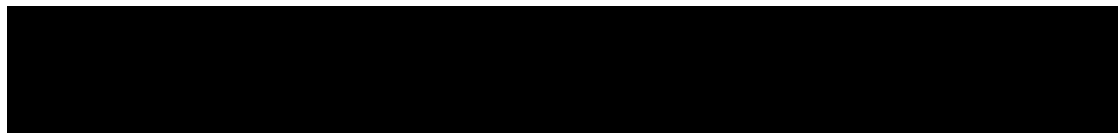
OS will be described using Kaplan-Meier curves with appropriate summary statistics.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort.

The overall observation period will be divided into three mutually exclusive segments:



1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by cohort. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and cohort.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (see NCI 2009), the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In cases (e.g. white blood cell differentials) the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the MAP and/or RAP.

10.5.3.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results have to be part of the CDP, MAP, CSP and RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

Data from other tests will be listed, notable values flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

Mood scales

Mood assessment includes two self-reported mood questionnaires, the GAD-7 Anxiety scale and PHQ-9 Depression scale. Shift tables comparing the baseline severity score to worst post-baseline severity score for each questionnaire will be provided.

10.5.3.5 Supportive analyses for secondary objectives

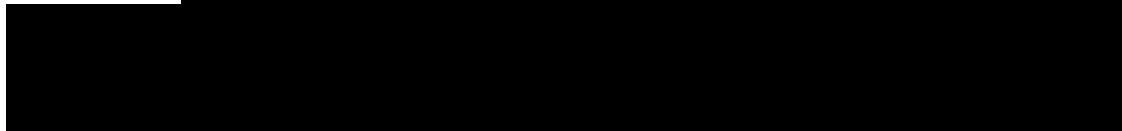
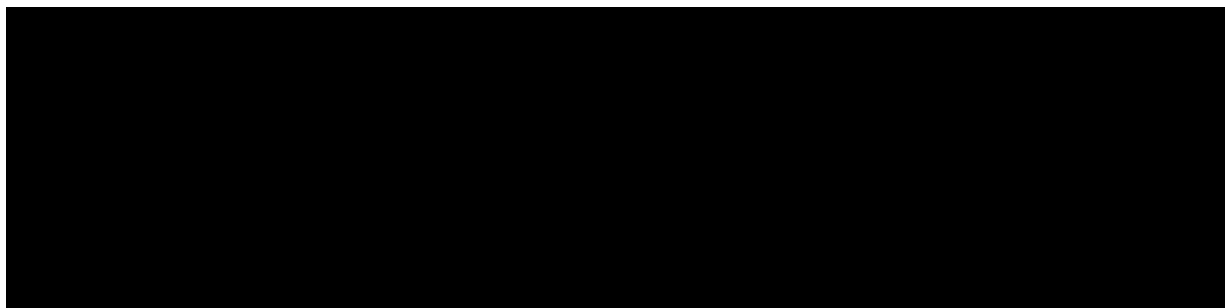
Not applicable.

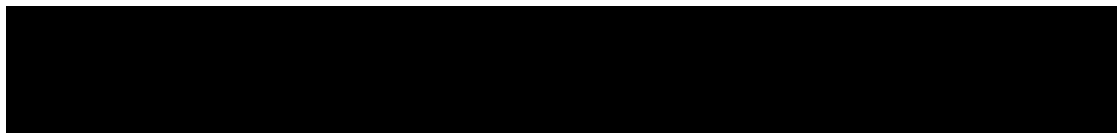
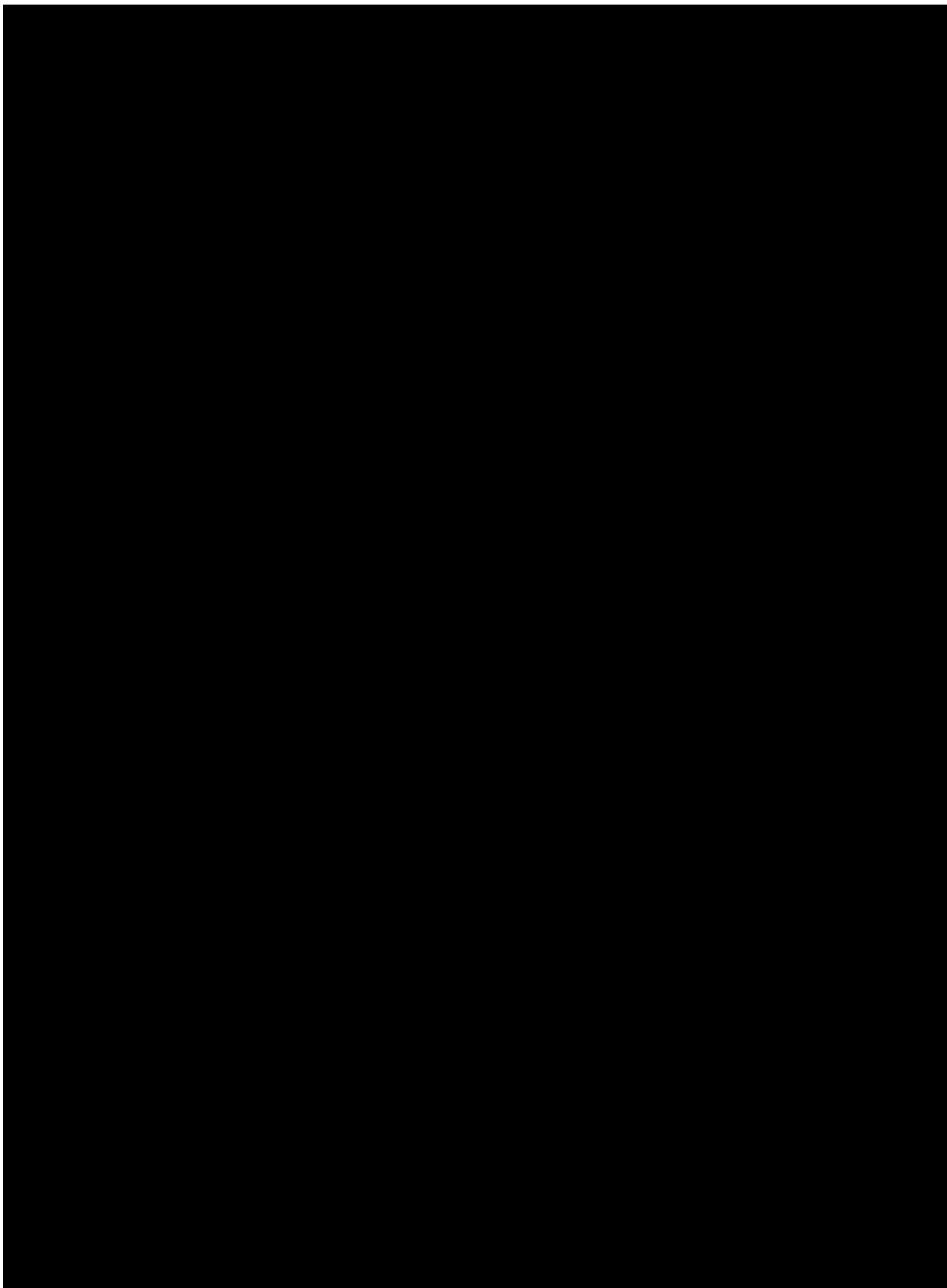
10.5.3.6 Tolerability

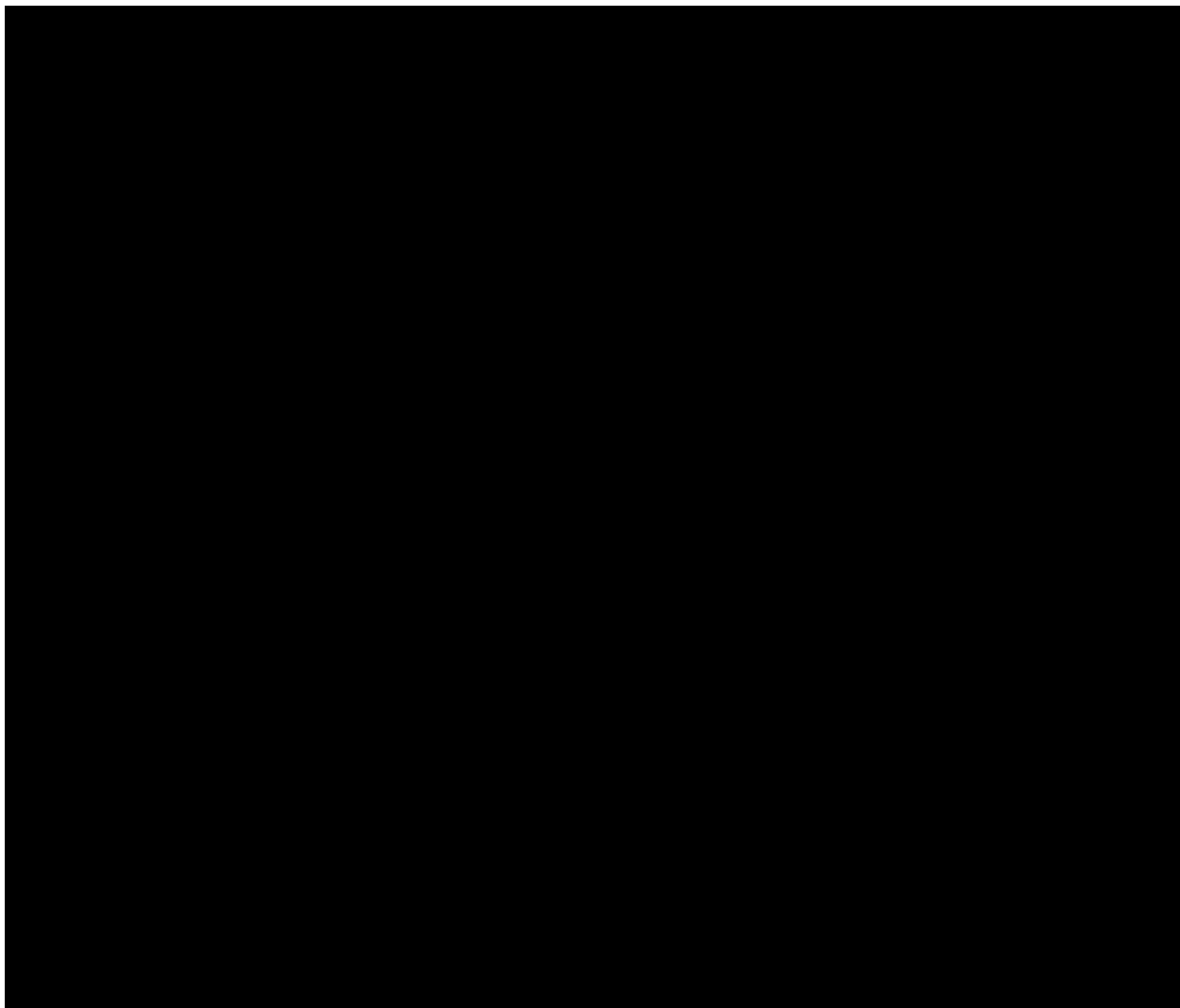
Not applicable.

10.5.4 Pharmacokinetics

Not applicable.







10.7 Interim analysis

Not applicable.

10.8 Sample size calculation

The analysis for each cohort will be based on an exact binomial test comparing the ORR to the reference level of 10% (null hypothesis). The test for each cohort will use a significance level of 5%. Sample size is determined in order to detect a true ORR of 35% with a probability of at least 80%. N=22 patients have to be included in each cohort in order to ensure this condition. A significant test result is achieved when at least 6 responses are observed among the 22 patients corresponding to a minimal observed ORR of 27.3%. Maximum number of patients per cohort will capped at N = 28 patients, in case of over enrollment. The following table provides the minimum number of responses (k) to be observed along with the corresponding number of patients enrolled (N) to achieve significant test result with corresponding power and observed ORR:



Table 10-1 Rejection criteria and power for different sample sizes

N	k	Power (%)	Observed ORR (%)
22	6	83.7	27.3
23	6	86.9	26.1
24	7	78.9	29.2
25	7	82.7	28.0
26	7	85.8	26.9
27	7	88.5	25.9
28	7	90.8	25.0

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient

source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 4](#).

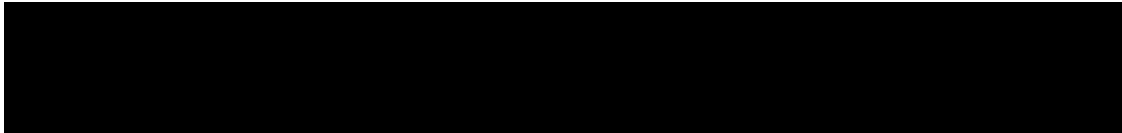
11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.



Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

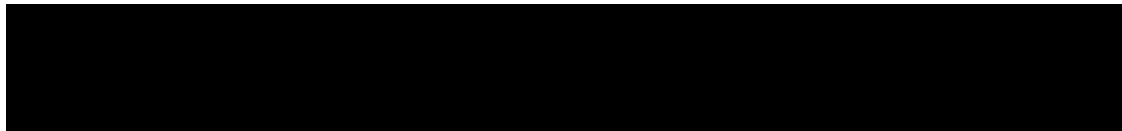
Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

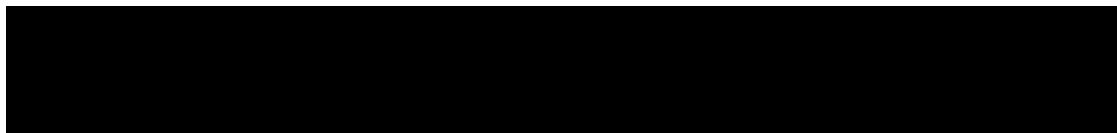
12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.



12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.



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14 Appendices

14.1 Appendix 1 - List of prohibited CYP3A inhibitors and inducers

Table 14-1 List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	carbamazepine *	felbamate *
conivaptan	aprepitant	phenobarbital *	topiramate * (>200 mg/day)
indinavir	atazanavir	phenytoin *	oxcarbazepin *
itraconazole	cimetidine	fosphenytoin *	eslicarbazepin *
ketoconazole	ciprofloxacin	primidone *	rufinamide *
lopinavir	darunavir	avasimibe	bosentan
mibefradil	diltiazem	rifabutin	efavirenz
nefazodone	elvitegravir	rifampin	etravirine
nelfinavir	erythromycin	St. John's Wort	modafenil
posaconazole	fluconazole		nafcillin
ritonavir	grapefruit juice		ritonavir
saquinavir	schisandra sphenanthera		talviraline
telithromycin	tipranavir		tipranavir
troleandomycin	tofisopam		
voriconazole	verapamil		
<p>* These drugs are Enzyme Inducing Anti-Epileptic drugs This database of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the University of Washington's Drug Interaction Database based on in vitro studies and from the FDA's "Guidance for Industry, Drug Interaction Studies;" and from (Pursche 2008).</p>			

14.2 Appendix 2 - List of CYP450 substrates to be used with caution

Table 14-2 List of CYP450 substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine	celecoxib	amitriptyline	adinazolam	felodipine ¹
cerivastatin	diclofenac	citalopram	alfentanil ^{1,2}	fentanyl ²
pioglitazone	flurbiprofen	clobazam	alpha-dihydroergocryptine ¹	flunitrazepam
repaglinide	fluvastatin	clomipramine	alprazolam	fluticasone ¹
rosiglitazone	glibenclamide (glyburide)	clopidogrel	amlodipine	lovastatin ¹
torasemide	gliclazide	diazepam	aripiprazole	maraviroc ¹
troglitazone	glimepiride	fluoxetine	atorvastatin	midazolam ¹
	glipizide	imipramine	brecanavir	nifedipine
	indomethacin	lansoprazole	brotizolam ¹	nisoldipine
	irbesartan	mephobarbital	budesonide ¹	nitrendipine
	ketobemidone	moclobemide	buspirone ¹	perospirone ¹
	lornoxicam	omeprazole	capravirine	quinine
	losartan	pantoprazole	cerivastatin	sildenafil ¹
	meloxicam	progesterone	chlorpheniramine	simvastatin ¹
	naproxen	quazepam	cyclosporine ²	sirolimus ^{1,2}
	nateglinide	rabeprazole	darifenacin ¹	tolvaptan
	piroxicam	sertraline	diazepam	trazodone
	rosiglitazone	S-mephenytoin	diergotamine ²	triazolam ¹
	S-ibuprofen		ebastine ¹	
	sulfamethoxazole		eletriptan ¹	
	tenoxicam		eplerenone ¹	
	tolbutamide		ergotamine ²	
	torasemide		estazolam	
	valdecoxib		everolimus ¹	

This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou 2009)

** CYP3A substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

¹ Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

² Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

14.3 Appendix 3 - List of prohibited QT prolonging drugs

Table 14-3 List of prohibited QT prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	CYP3A4 substrate with narrow therapeutic index.
Bepidil	known risk for TdP	
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	CYP3A substrate with narrow therapeutic index.
Disopyramide	known risk for TdP	
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	
Droperidol	known risk for TdP	
Halofantrine	known risk for TdP	
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	
Levomethadyl	known risk for TdP	Sensitive CYP3A substrate
Mesoridazine	known risk for TdP	
Methadone	known risk for TdP	
Pentamidine	known risk for TdP	
Pimozide	known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Probuco	known risk for TdP	
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Sensitive CYP3A substrate
Quinidine	known risk for TdP	Sensitive CYP3A substrate
Sotalol	known risk for TdP	
Sparfloxacin	known risk for TdP	
Tacrolimus	possible risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	Known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Sensitive CYP3A substrate

(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT

Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Please also refer to <http://crediblemeds.org/> for a comprehensive list of agents that prolong the QT interval

14.4 Appendix 4 - List of QT prolonging drugs to be used with caution

Table 14-4 List of QT prolonging drugs to be used with caution

Drug	QT risk
Alfuzosin	possible risk for Torsades de Pointes
Amantadine	possible risk for Torsades de Pointes
Amitriptyline	conditional risk for Torsades de Pointes
Azithromycin	possible risk for Torsades de Pointes
Chloral hydrate	possible risk for Torsades de Pointes
Citalopram	conditional risk for Torsades de Pointes
Clomipramine	conditional risk for Torsades de Pointes
Clozapine	possible risk for Torsades de Pointes
Desipramine	conditional risk for Torsades de Pointes
Diphenhydramine	conditional risk for Torsades de Pointes
Dolasetron	possible risk for Torsades de Pointes
Doxepin	conditional risk for Torsades de Pointes
Dronedarone	possible risk for Torsades de Pointes
Felbamate	possible risk for Torsades de Pointes
Flecainide	possible risk for Torsades de Pointes
Fluoxetine	conditional risk for Torsades de Pointes
Foscarnet	possible risk for Torsades de Pointes
Fosphenytoin	possible risk for Torsades de Pointes
Galantamine	conditional risk for Torsades de Pointes
Gatifloxacin	possible risk for Torsades de Pointes
Gemifloxacin	possible risk for Torsades de Pointes
Granisetron	possible risk for Torsades de Pointes
Imipramine	conditional risk for Torsades de Pointes
Indapamide	possible risk for Torsades de Pointes
Isradipine	possible risk for Torsades de Pointes
Levofloxacin	possible risk for Torsades de Pointes
Lithium	possible risk for Torsades de Pointes
Mexiletine	conditional risk for Torsades de Pointes
Moexipril/HCTZ	possible risk for Torsades de Pointes
Moxifloxacin	possible risk for Torsades de Pointes
Nicardipine	possible risk for Torsades de Pointes
Nortriptyline	conditional risk for Torsades de Pointes
Octreotide	possible risk for Torsades de Pointes
Ofloxacin	possible risk for Torsades de Pointes
Ondansetron	possible risk for Torsades de Pointes
Oxytocin	possible risk for Torsades de Pointes
Paliperidone	possible risk for Torsades de Pointes
Paroxetine	conditional risk for Torsades de Pointes
Perflutren lipid microspheres	possible risk for Torsades de Pointes
Protriptyline	conditional risk for Torsades de Pointes

Drug	QT risk
Ranolazine	possible risk for Torsades de Pointes
Risperidone	possible risk for Torsades de Pointes
Roxithromycin*	possible risk for Torsades de Pointes
Sertindole	possible risk for Torsades de Pointes
Sertraline	conditional risk for Torsades de Pointes
Solifenacin	conditional risk for Torsades de Pointes
Tizanidine	possible risk for Torsades de Pointes
Trazodone	conditional risk for Torsades de Pointes
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes
Trimipramine	conditional risk for Torsades de Pointes
Venlafaxine	possible risk for Torsades de Pointes
Ziprasidone	possible risk for Torsades de Pointes

(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT
Please also refer to <http://crediblemeds.org/> for a comprehensive list of agents that prolong the QT interval.

14.5 Appendix 5 - Guideline for efficacy evaluation in lymphoma studies (based on Cheson response criteria)

14.5.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy in Oncology Lymphoma studies where Cheson response criteria apply.

This document is based on the International Working Group response criteria ([Cheson et al 1999](#)), and the International Harmonization Project revised response criteria ([Cheson et al 2007b](#)). Further clarification on these criteria has been published by ([Cheson 2007a](#)).

As Positron emission tomography (PET) is not yet widely accepted ([Cheson 2009](#)) for assessing response to treatment in lymphoma it is not considered for standard use in Novartis Oncology Lymphoma studies and therefore it is not considered in this document.

In general, this document is intended for studies where patients currently have measurable disease to be assessed, and therefore does not specifically address studies when the eligible patient population has no measurable disease (such as studies in patients who achieved complete response to first line treatment, or in post-transplantation settings). However, this guidance should be readily adaptable to these settings (see [Appendix E](#)).

As these are general guidelines, the following adjustments will apply to this trial:

- Randomization is not applicable to the study since it is a non-randomized trial. All responses will be calculated from start of treatment.
- If a lesion splits during the study, the sub-lesions will not be measured separately. Instead, such lesions which have split into sub-lesions will be measured as one lesion with all sub-lesions contributing to the overall SPD.
- Central Blinded Review of radiological response will not be used for this study. Responses will be assessed by the Investigator.

14.5.2 Definitions and criteria for normalization

14.5.2.1 Definitions

Throughout this document, the following definitions will apply (See also [Appendix A](#)).

Nodal vs extranodal lesion

A lesion is categorized based on the location as:

- **Nodal lesion**,
- **Extranodal lesion**, if it is located in organs other than lymph node or nodal mass, but including spleen and liver.

Measurability

Throughout this document, a lesion will be called **measurable** if it can be measured accurately in 2 perpendicular dimensions and:

- For nodal lesion, if the long axis is > 15 mm, regardless of the length of the short axis,
- For extranodal lesion, if the long and short axes are ≥ 10 mm.

Classification of lymph nodes

Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement above will constitute a **measurable nodal lesion**.
- A lymph node not meeting the measurability requirement but with long axis > 15 mm (e.g. short axis can not be measured accurately) will constitute a non-measurable nodal lesion.
- A lymph node not meeting the measurability criteria but with a size of 11 mm to 15 mm in the long axis and > 10 mm in the short axis will be checked for relationship to disease:
 - If it is thought to be disease related, it will constitute a **non-measurable nodal lesion** (referred to as “involved node” in [Cheson et al 2007b](#)).
 - If it is not thought to be disease related, it will constitute an **abnormal lymph node** but not a lesion.
- All other lymph nodes will be considered normal and will not constitute nodal lesions.

14.5.2.2 Criteria for normalization of lesions

The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤ 10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

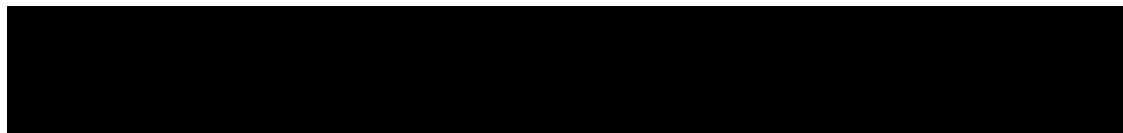
14.5.3 Efficacy assessments

14.5.3.1 Eligibility

Studies will be intended to include patients with measurable disease.

Patients should have at least **one measurable nodal lesion greater than 20 mm** in the long axis.

In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at baseline, then the patient must have at least one measurable extranodal lesion.



14.5.3.2 Methods of disease assessment

All radiological measurements should be taken in two perpendicular dimensions and recorded in metric notation, using a ruler or calipers.

All baseline evaluations should be performed as closely as possible to the randomization/start of treatment (preferably within 7 days) and never more than **3 weeks (21 days)** before the randomization/start of treatment.

14.5.3.2.1 CT scan (or MRI)

For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If at baseline a patient is known to be allergic to CT contrast or develops allergy during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (eg. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a “Unknown” overall radiological response assessment. However, another overall radiological response than the Novartis calculated “Unknown” response may be accepted from the investigator or the central blinded reviewer if a definitive overall radiological response can be justified to be based on the available information.

In order to calculate the sum of the product of the diameters (SPD) of all index lesions (or extranodal lesions), their size must be entered throughout the study.

Actual lesion measurements should be entered on the corresponding CRFs. If, during the course of the study, either of the perpendicular diameters of a lesion can not be reliably measured because of its small size, it is recommended to enter the minimum limit of detection as the diameter size (e.g. 5 mm for spiral CT). In other cases when, during the course of the study, the diameter cannot be reliably measured for reasons other than its size (i.e. borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

If lesions become confluent over time, it is recommended to measure them as one lesion, report the overall diameters to one of the lesions and assign 0 mm x 0 mm to each of the other previously measured lesions. If a lesion splits during the study, each sub-lesion should be measured separately for all subsequent assessments and all sub-lesions contribute to the SPD.

14.5.3.2.2 Bone marrow assessment

Documentation of status of bone marrow involvement by lymphoma based on prior bone marrow biopsy or aspirate findings is required at baseline for all patients.

If no such documentation is available then a bone marrow biopsy or aspirate should be performed at baseline.

If bone marrow involvement is assessed by biopsy, the biopsy sample should have a goal of > 20 mm unilateral core. If the biopsy sample is indeterminate by morphology (immunohistochemistry), then flow cytometry may be performed on bone marrow aspirate to confirm the findings.

14.5.3.2.3 Physical examination and assessment of B-symptoms

Skin lesions, if the size is ≥ 20 mm in at least one diameter, must be histologically confirmed for lymphoma involvement (the investigational site must document the histological confirmation (yes or no) on the corresponding CRF) and photographed including a ruler (color photography using digital camera). Tumor assessment will be performed and results will be recorded on the corresponding CRF at baseline and at the time of each radiological assessment.

B-symptoms are of importance in determining prognosis and should resolve completely in patients who have achieved complete response. B-symptoms in lymphoma patients are disease related clinical symptoms and are not caused by anticancer therapy (or drug toxicity).

B-symptoms are defined as follows:

- Significant unexplained fever ($\geq 38^{\circ}\text{C}$),
- Unexplained, recurrent drenching night sweats
- Unexplained loss of > 10% body weight within the previous 6 months, as assessed and reported (present vs. absent) by the Investigator.

14.5.3.3 Documentation of disease

For the evaluation of disease at baseline and throughout the study, the following are recorded.

Index nodal lesions

Index nodal lesions are selected from the measurable nodal lesions. A minimum of one measurable index nodal lesion and maximum of six of the largest dominant nodal lesions should be documented at baseline and assessed throughout the study. If a patient has no measurable nodal disease at baseline, then it would be acceptable that no index nodal lesions be identified. Index nodal lesions should be from disparate regions of the body including mediastinal and retroperitoneal areas of disease whenever these sites are involved. Two perpendicular dimensions must be recorded on the corresponding CRF at each assessment of a measurable lesion selected to be an index lesion.

Non-index nodal lesions

All other nodal lesions (both measurable and non-measurable) are considered as non-index lesions.

Non-index lesions should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in [Section 14.5.3.4.2](#).

Spleen and liver (index and non-index) lesions

The spleen and liver will be assessed by CT scan (or MRI scan).

A maximum four of the largest dominant measurable nodules representing all involved anatomic locations should be selected as splenic and hepatic index lesions to be measured at baseline and followed up during the treatment. Two perpendicular dimensions will be recorded into the CRF at each assessment.

All other splenic or hepatic nodules (both measurable and non-measurable) are considered as non-index lesions. They should be documented at baseline and assessed throughout the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in [Section 14.5.3.4.2](#).

Other extranodal (index and non-index) lesions

Organs other than lymph nodes, liver, spleen and bone marrow (such as breast and lung) can be occasionally involved by lymphoma. Determination of lymphoma involvement of these organs should be confirmed histologically.

If such organs are confirmed to be involved with measurable lesions, then index lesions should be selected from those organs. Up to four measurable lesions will be selected as index extranodal lesions from disparate regions (other than liver and spleen) at baseline and followed during the study.

Additional measurable lesions and all non-measurable extranodal disease will be documented at baseline and assessed throughout the study as non-index lesions. Other non-measurable disease, such as pleural effusion or bone lesions that are documented to be due to malignant disease, will be recorded at baseline as non-index lesions and followed during the study. Measurements of these lesions are not required to be documented on the CRF. Their response status will be determined from investigator assessment as described in [Section 14.5.3.4.2](#).

Enlarged spleen or liver

The presence of enlarged spleen or liver before randomization/start of treatment on the basis of CT scan should be recorded on the corresponding CRF at baseline, and reassessed if the patient has a radiological CR.

Bone marrow involvement

Status of bone marrow involvement by lymphoma before randomization/start of treatment will be collected (see [Section 14.5.3.2.2](#)).

B-symptoms

B-symptoms (unexplained fever $\geq 38^{\circ}\text{C}$; unexplained, recurrent drenching night sweats; unexplained loss of $> 10\%$ body weight within the previous 6 months) will be recorded before randomization/start of treatment (baseline) and reevaluated if patients have achieved radiological CR as well as at the end of therapy.

14.5.3.4 Evaluation of radiological response

For the sake of simplicity, complete remission (as defined in [Cheson et al 2007b](#)) and complete response will both be referred to as complete response in this document.

To evaluate disease response to treatment, all index and non-index lesions will be followed and assessed throughout the study. At each assessment, response is evaluated separately for the **index lesions** ([Table 14-7](#)) and **non-index lesions** ([Table 14-8](#)) identified at baseline, then a combined overall radiological response is determined ([Table 14-9](#)).

14.5.3.4.1 Evaluation of index lesions (nodal and extranodal)

(a) When index nodal lesions are not in complete response

The response for index lesions is evaluated by calculating the Sum of the Products of Diameters (SPD) of all index lesions (see [Table 14-5](#)), except when there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions) (see [Section b](#) below).

Table 14-5 Radiological status based on SPD calculation for all index lesions

Response Criteria ¹	Evaluation of index lesions
Complete Response (CR)	See Table 14-7 below (not based on SPD calculation for all index lesions)
Partial Response (PR)	At least 50% decrease from baseline in the SPD of all index lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir ² in the SPD of all index lesions
¹ At each assessment (if the index nodal lesions are not in CR status), the response status based on SPD calculation will be first assessed for meeting PD status criteria, then PR status and SD status. ² Nadir is defined as the smallest sum of the product of the diameters of all index lesions recorded so far, at or after baseline.	

(b) When index nodal lesions are in complete response

When there is a Complete Response for index nodal lesions (i.e. complete normalization of all index nodal lesions as defined in [Section 14.5.2.2](#): all index lesion ≤ 15 mm in long axis), the SPD for these index nodal lesions may not be equal to zero and therefore a calculation of a SPD for all index lesions may be misleading. Therefore, by default, a specific response for extranodal index lesions needs to be evaluated, based on the SPD calculation restricted to all index extranodal lesions only (see [Table 14-6](#)).

Table 14-6 Radiological response criteria for index extranodal lesions in case of CR in index nodal lesions

Response Criteria ¹	Evaluation of index extranodal lesions
Complete Response (CR)	Complete disappearance of all index extranodal lesions
Partial Response (PR)	At least 50% decrease from baseline in the SPD restricted to all index extranodal lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR or PR and failure to fulfill the criteria for PD
Progressive Disease (PD)	At least a 50% increase from nadir ² in the SPD restricted to all index extranodal lesions
¹ At each assessment, response will be first assessed for meeting CR status. If CR status is not met, response will be assessed for PD status, then PR status and SD status. ² Nadir is defined as the smallest sum of the product of the diameters restricted to all index extranodal lesions recorded so far, at or after baseline.	

The algorithm for evaluating the response integrating index extranodal lesions and the SPD calculated on all index lesions (where appropriate) provides an overall response for index lesions (see [Table 14-7](#)).

(c) Evaluation of response for all index lesions

The evaluation of response for all index lesions is based on the combination of the response for index nodal lesions (CR or non-CR), the response for index extranodal lesions (as calculated in [Table 14-6](#)), and the status based on the SPD calculated on all index lesions (nodal and extranodal), as described in [Table 14-7](#) and [Appendix B](#).

Table 14-7 Radiological response for index lesions

Response for index nodal lesions ¹	Response for index extranodal lesions ¹	Status based on SPD calculation for all index lesions	Response for index lesions
CR	CR	Not calculated	CR
CR	SD/ PR	Not calculated	PR
CR	PD	PD	PD
CR	PD	PR	PR
CR	PD	SD	SD
Non-CR	Not evaluated	PD	PD
Non-CR	Not evaluated	PR	PR
Non-CR	Not evaluated	SD	SD
¹ If no index nodal lesions are present at baseline, then index lesions response is equal to the index extranodal lesions response. A similar rule applied if no index extranodal lesions are present at baseline, then index lesions response is equal to the index nodal lesions response.			

In case of a missing measurements of any of the index lesions, the radiological response for index lesions at that assessment will be “Unknown (UNK)”, unless progression was seen.

All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for index lesions at that assessment will be “Unknown (UNK)”.

14.5.3.4.2 Evaluation of non-index lesions (including nodal, splenic and/or hepatic nodules and other extranodal lesions)

At each reassessment, a non-index lesion (or a group of non-index lesions) will be given one of the following designations:

- Normalization (non-index nodal lesion has regressed to normal size; non-index extranodal lesion is no longer present). Normalization of non-index nodal lesions should be determined based on their size at baseline as described in [Section 14.5.2.2](#).
- Improved, stable or worsened, but without unequivocal evidence of disease progression (non-index lesion is present but there is not sufficient worsening to declare PD based on the existing non-index lesions).
- Unequivocal evidence of disease progression (worsening of existing non-index lesions is sufficient to declare PD)
- Not assessed

Then, this status for each non-index lesion (or group of non-index lesions) will lead to a global response for non-index lesions (Table 14-8 and [Appendix C](#)):

Table 14-8 Response criteria for non-index lesions (nodal, splenic and/or hepatic nodules and other extranodal lesions)

Response Criteria	Evaluation of non-index lesions
Complete Response (CR)	Complete normalization of all non-index nodal and extranodal lesions: Radiological regression to normal size of all lymph nodes and complete disappearance of all extranodal (including splenic and/or hepatic nodules) lesions
Stable Disease (SD)	Failure to attain the criteria needed for CR and failure to fulfill the criteria for PD
Progressive Disease (PD)	Unequivocal disease progression of any existing non-index lesions (nodal or extranodal)

In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be “Unknown (UNK)”, unless progression was seen.

All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for non-index lesions at that assessment will be “Unknown (UNK)”.

14.5.3.4.3 New lesions

The appearance of any new nodal lesion >15 mm in any axis.

New nodal lesion is defined by:

- either a previously normal lymph node becoming > 15 mm in any axis,
- or a previously identified abnormal lymph node showing an increase of at least 50% in the long axis,
- as assessed by investigator (or Central Review if applicable)

OR

- any discrete extranodal (including splenic and/or hepatic nodules) lesions reliably appearing on CT scan or MRI after baseline is always considered as Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the CRF.

Determination of new lymphoma involvement in organs other than lymph nodes or liver or spleen should be confirmed histologically and the site must document that in a comment to the corresponding CRF.

14.5.3.4.4 Overall radiological response

Overall radiological response is calculated as shown in Table 14-9.

Table 14-9 Overall radiological response at each assessment

Index lesions	Non-index lesions ¹	New lesions	Overall radiological response
CR	CR	No	CR
CR	SD	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
¹ If no non-index lesions are present at baseline, then this column is not used in evaluating overall radiological response.			

If the evaluation of any of the index or non-index lesions identified at baseline could not be made during follow-up or if the index or non-index response is “Unknown (UNK)”, the overall response status at that assessment must be “Unknown (UNK)” unless progression or a new lesion was seen.

14.5.3.5 Evaluation of overall disease response

The evaluation of overall disease response at each assessment is a composite of the individual radiological responses (index and non-index lesions, new lesions), laboratory test (bone marrow) and clinical responses (lymphoma related clinical symptoms).

14.5.3.5.1 Bone marrow re-assessment at time of radiological CR

In order to confirm a Complete disease response (CR), bone marrow biopsy or aspirate may be required when a radiological CR has been achieved (see [Section 14.5.3.2.2](#)). Details are provided in the Study Protocol. The infiltrate of lymphoma in bone marrow must have cleared on repeat bone marrow biopsy or aspirate. Patients who achieve a CR by other criteria but who have persistent morphologic positive or inconclusive bone marrow involvement will be considered partial responders. New or recurrent bone marrow involvement anytime during the follow up will be considered PD. Bone marrow biopsy or aspirate will be performed after the first assessment of CR or when clinically indicated.

The biopsy sample of bone marrow must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry.

14.5.3.5.2 Overall disease response

If a patient has an overall radiological response of CR as defined in [Table 14-9](#), then this response must be confirmed by bone marrow biopsy or aspirate (if required as per the Study Protocol), presence of normal liver and spleen size, and evaluation of lymphoma related B-symptoms. The patient's overall response will be calculated as follows (see also [Appendix D](#)):

A patient will be deemed to have overall disease response of CR if bone marrow biopsy or aspirate becomes negative for tumor involvement (if the bone marrow was involved by lymphoma at baseline) and the liver and spleen are normal in size and there are no lymphoma related B-symptoms in addition to radiological CR.

If assessments of any of the following: lymphomatous infiltration of bone marrow (If required as per the Study Protocol), or evaluation of B-symptoms is not done, unknown or indeterminate or B-symptoms are still present when the overall radiological response is assessed as CR or the liver or spleen are enlarged, then the overall disease response will be assessed as PR until evaluation of these factors have shown normalized results and recorded on the corresponding CRF.

For patients whose radiological response is anything other than CR, assessment of bone marrow, liver, spleen and B-symptoms will not be required in evaluating overall response and overall disease response is the same as radiological response. However any new or recurrent bone marrow involvement at any time during follow-up will be considered PD.

Of note, appearance of B-symptoms or enlarged spleen or liver will not in themselves constitute documentation of progression. They are however expected to be associated with progressive disease. Every effort should be made to document that evidence radiologically and report the corresponding tumor assessments. Such tumor assessments are expected to be performed within 2 months of appearance of B-symptoms or enlarged spleen or liver.

14.5.4 Efficacy analysis definitions

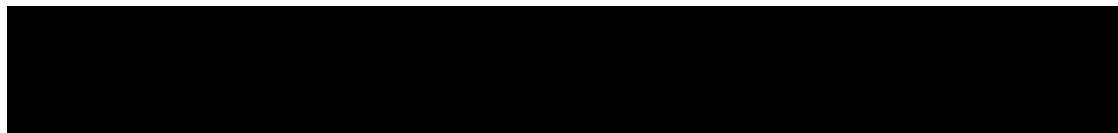
14.5.4.1 Best overall disease response

The best overall disease response is the best disease response recorded from randomization/start of treatment until progressive disease or start of new anticancer therapy, whichever comes first.

A best overall disease response of SD will be declared when at least one SD assessment is available at least 6 weeks after randomization/start of treatment (and the patient would not qualify for CR or PR).

A patient will have a best overall disease response of PD if the progressive disease was observed less than 17 weeks after randomization/ start of treatment (and the patient does not qualify for CR, PR or SD).

The best overall disease response for a patient is always calculated, based on the sequence of overall disease responses. However, the overall disease response at a given assessment may be provided from different sources:



- Investigator overall disease response based on local radiological assessments, clinical and pathological (bone marrow in patients with CR) response
- Central Blinded Review of radiological response, with or without blinded adjudication integrating clinical and pathological (bone marrow in patients with CR) response
- Novartis calculated overall disease response, based on measurements / lesion status from either Investigator or Central Review and clinical and pathological (bone marrow in patients with CR) response

Based on the patients' best overall disease response during the study, the following rate is then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall disease response of CR and PR.

14.5.4.2 Time to event variables

Most of the time to event variables are defined in this section according to the International Working Group response criteria ([Cheson et al 2007b](#)). Further details on dates and censoring rules are provided respectively in [Section 14.5.4.3](#) and [Section 14.5.4.4](#).

14.5.4.2.1 Overall survival

Overall survival (OS) is defined as the time from the date of randomization/start of treatment to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact.

14.5.4.2.2 Progression-free survival

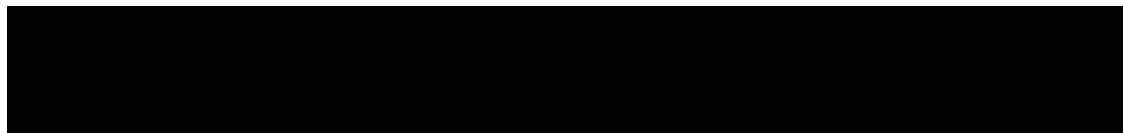
Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.

14.5.4.2.3 Time to progression

Time to progression (TTP) is defined as the time from the date of randomization/start of treatment to the date of first documented progression or death due to lymphoma. If a patient has not had an event, time to progression is censored at the date of the last adequate assessment.

14.5.4.2.4 Duration of response

Duration of overall response (CR or PR) applies only to patients whose best overall disease response was CR or PR. It is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.



Duration of overall complete response (CR) applies only to patients whose best overall disease response was CR. It is defined as the time from the date of first documented disease complete response to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall complete response is censored at the date of the last adequate assessment.

14.5.4.2.5 Time to response

Time to overall disease response (CR or PR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease response (PR or CR). This analysis will include all patients/responders. If all patients are included, then patients who did not achieve a PR or CR will be censored:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise.

Time to overall disease complete response (CR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease complete response (CR). This analysis will include all patients/responders. If all patients are included, then patients who did not achieve a CR will be censored:

- At maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause)
- At the date of the last adequate assessment otherwise.

14.5.4.2.6 Lymphoma specific survival

Lymphoma specific survival (LSS) is defined as the time from the date of randomization/ start of treatment to the date of death documented as a result of lymphoma. If a patient has not had an event, lymphoma specific survival will be censored:

- at the date of last contact if the patient is not known to have died,
- at the date of death if the patient died for other reason than lymphoma.

14.5.4.2.7 Event free survival

Event-free survival (Time to treatment failure (TTF)) is defined as the time from the date of randomization to the earliest date of any of the following:

- death
- progressive disease as overall disease response assessed by the local investigator prior to treatment discontinuation
- study treatment discontinuation due to:
 - disease progression
 - adverse event(s)
 - abnormal laboratory value(s)
 - abnormal test procedure results
 - subject withdrew consent

- lost to follow-up
- death
- new cancer therapy

Patients who discontinue study treatment for reasons other than those listed above (i.e., as a result of protocol violation, administrative problems) are censored at the date of the last adequate assessment prior to discontinuation. Patients with neither an event nor study treatment discontinuation are censored at the date of the last adequate assessment.

14.5.4.3 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as:

- the latest date of all radiological measurement dates (e.g. CT-scan (or MRI), and excluding both bone marrow biopsy and B-symptoms assessment), if the overall disease response at that assessment is CR/PR/SD/UNK,
- the earliest date of all measurement dates (e.g. CT-scan (or MRI), including bone marrow biopsy, but excluding B-symptoms assessments) if the overall disease response at that assessment is PD.

Start dates

For all “time to event” variables, other than the duration of responses, the date of randomization /start of treatment will be used as the start date.

For the calculation of duration of responses the following start date should be used:

- **Date of first documented response** is the assessment date of the first overall disease response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively.

End dates

The end dates which are used to calculate ‘time to event’ variables are defined as follows:

- **Date of death** as reported on the CRF (on the treatment completion page, the study evaluation completion page or survival follow-up page).
- **Date of last contact** is defined as the last date the patient was known to be alive as derived from different CRF pages (see details in [Section 14.5.5](#)).
- **Date of progression** is the first assessment date at which the overall disease response was recorded as PD.
- **Date of last adequate assessment** is the date the last assessment with overall disease response of CR, PR or SD which was made before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.

- **Date of next scheduled assessment** is the date of the last adequate assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next radiological assessment as per protocol.
Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.
- **Date of treatment discontinuation** is the last known date subject took study drug.
- **Date of secondary anti-cancer therapy** is defined as the start date of first additional (secondary) antineoplastic therapy or surgery (see details in [Section 14.5.5](#))

14.5.4.4 Censoring and sensitivity analyses

14.5.4.4.1 Censoring reasons

This section outlines the possible censoring reasons for each time to event variables. In order to summarize the various reasons for censoring, the following categories ([Table 14-10](#)) will be calculated for each time to event variable based on the information reported on treatment completion page, the study evaluation page and the survival page.

Table 14-10 Censoring reasons

Time to event variables	Possible censoring reasons
OS	Alive
	Lost to follow-up
PFS, TTP and duration of response	Ongoing without event
	Lost to follow-up
	Withdrew consent
	Death due to reason other than lymphoma (only used for TTP and duration of response)
	New anti-cancer therapy added (optional, see Table 14-11)
	Event documented after two or more missing tumor assessments (optional, see Table 14-11)
	Adequate assessment no longer available ¹
LSS	Alive
	Lost to follow-up
	Death due to reason other than lymphoma
TTF	Ongoing without event
	Discontinuation for protocol deviation
	Discontinuation for administrative problems
	Study completed as per protocol
	Event documented after two or more missing tumor assessments
	Adequate assessment no longer available ¹
¹ Adequate assessment is defined in Section 14.5.4.3 . This reason corresponds to any censoring reasons after two or more missing tumor assessments. This reason will also be used for censor in case of no baseline assessment	

14.5.4.4.2 Event date, censoring date and sensitivity analyses

This section outlines the possible event and censoring dates for progression (Table 14-11), as well as addressing the issues of missing tumor assessments during the study. It is important that the protocol and analysis plan specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.5.4.2, and using the draft FDA guideline on endpoints (FDA Guideline 2005) (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-11 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression) ¹ (1) = default unless specified differently in the protocol or analysis plan	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment ²	Censor
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment ¹	Event Event
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment ¹	Event Event
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment ¹ (2) Date of next scheduled assessment ¹ (3) Date of progression (or death)	Censor Event Event
D	No progression	(1) Date of last adequate assessment	Censor
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Event
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censor Censor Event Ignored
G	Deaths due to reason other than lymphoma	(1) Date of last adequate assessment	Censor (only TTP and duration of response)

¹ = Definitions can be found in Section 14.5.4.3.

² = The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or more missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity

analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to ‘Disease progression’ without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

- Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g.: By assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in [Table 14-11](#) the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

Date of previous scheduled assessment (from baseline) is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate assessment.

- By considering any appearance or recurrence of B-symptoms or enlarged spleen/liver as a documented progression with a date of progression being the one of those symptoms.

The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the Study Protocol or RAP documentation.

14.5.5 Data handling and programming conventions

The following could be used for programming of efficacy results, but should be specified in the RAP documentation:

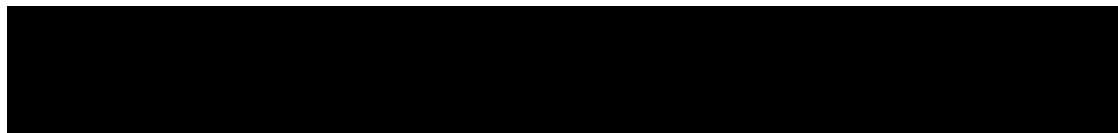
Calculation of ‘time to event’ variables

Time to event = end date – start date + 1 (in days)

When no post-baseline assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last assessment, i.e. time to event variables can never be negative.

Date of last contact

The date of last contact will be derived for patients alive using the latest complete date among the following:



- All assessment dates (e.g. vital signs assessment, performance status assessment, and also assessment date in third-party data such as tumor imaging, central laboratory, ECG etc.)
- Medication dates including study medication, concomitant medications, antineoplastic therapies administered after study treatment discontinuation.
- Adverse events dates
- Last contact date collected on the 'Survival information' eCRF.
- Randomization date.

Date of secondary anti-cancer therapy

The date of secondary anti-cancer therapy is the date of the 1st antineoplastic therapy or surgery reported in the concomitant medications page, further antineoplastic therapy page or from other sources (e.g. Dosage administration record page).

Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in [Section 14.5.4.3](#)). If all measurement dates have no day recorded, the 1st of the month is used.

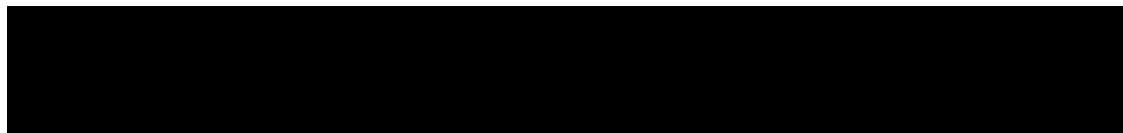
If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Incomplete dates for last contact or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

Study/project specific programming

The standard analysis programs need to be adapted for each study/project.



14.5.6 References (available upon request)

- Cheson BD (2007a) The international harmonization project for response criteria in lymphoma clinical trials. *Hematol Oncol Clin N Am* 21:841-854.
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- Cheson BD, Horning SJ, Coiffier B, et al (1999) Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 17:1244-1253.
- Cheson BD, Pfistner B, Juweid ME, et al (2007b) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586.
- FDA Guideline (2005) Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.
- Pursche S, Schelever E, von Bonin M, et al (2008) Influence of enzyme-inducing antiepileptic drugs on trough level of imatinib in glioblastoma patients. *Curr. Clin. Pharmacol*; 3 (3): 198-203
- Zhou S-F, Liu J-P, Chowbay B (2009) Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metabolism Reviews*; 41(2): 89-295

14.5.7 Appendices

Figure 14-1 Appendix A - Definition of index nodal lesion, non-index nodal lesion, index extranodal lesion, non-index extranodal lesion

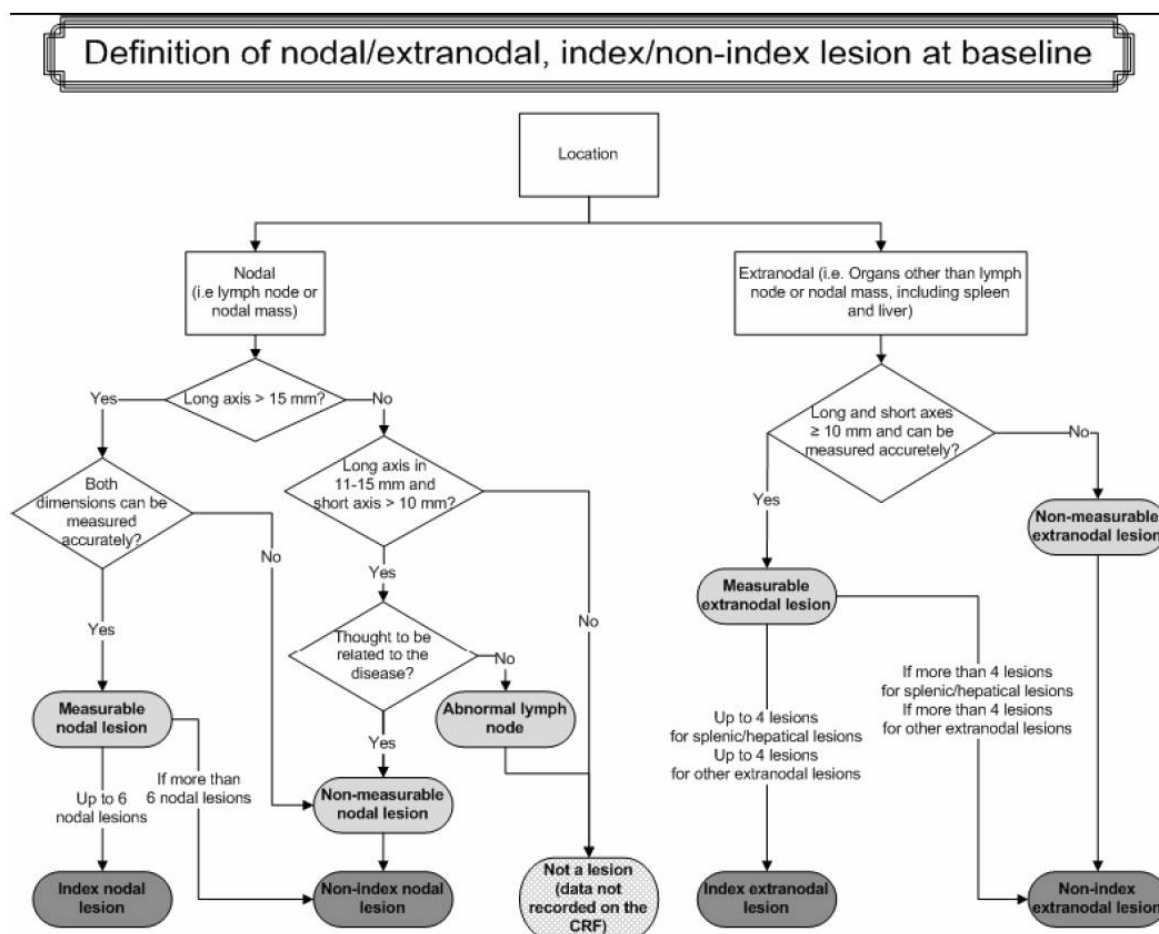
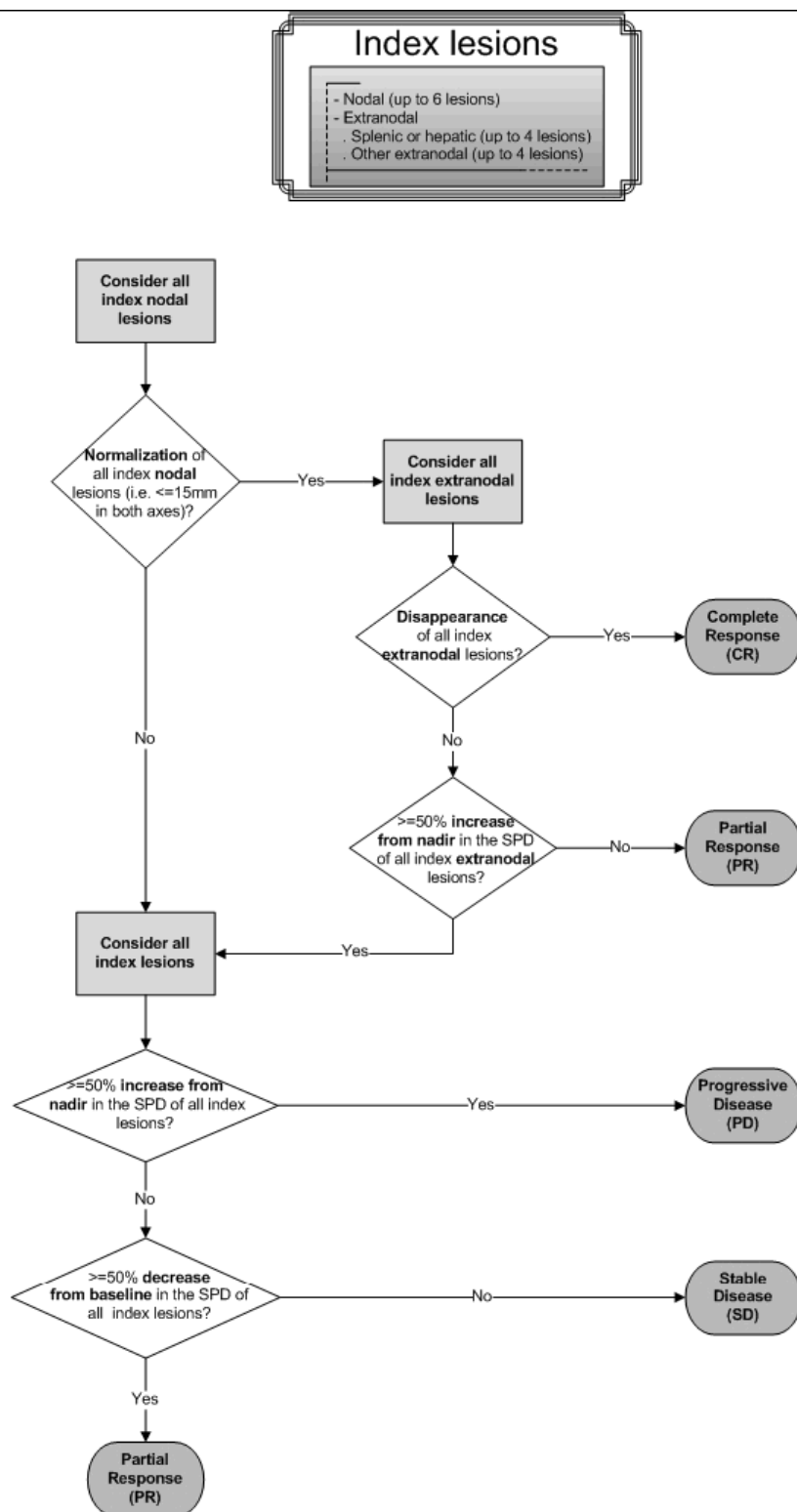


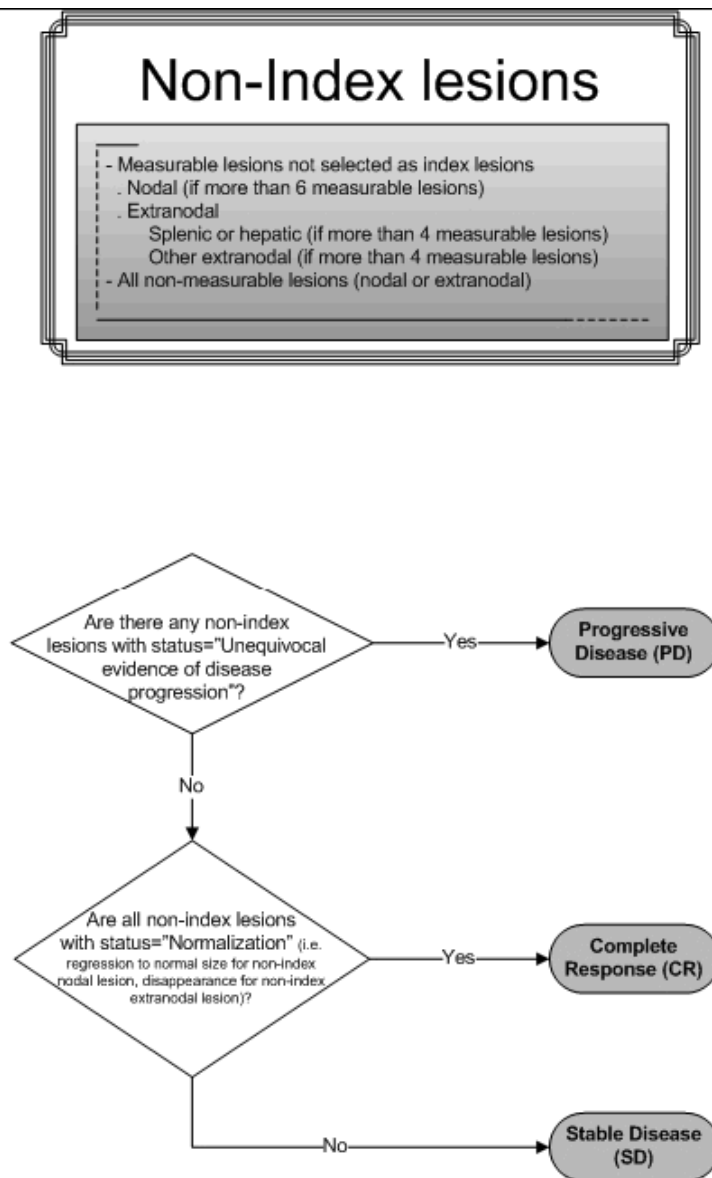
Figure 14-2 Appendix B - Calculation of the response for index lesions



Notes:

1. In case of a missing measurement of any of the index lesions, the radiological response for index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for index lesions at that assessment will be "Unknown (UNK)".

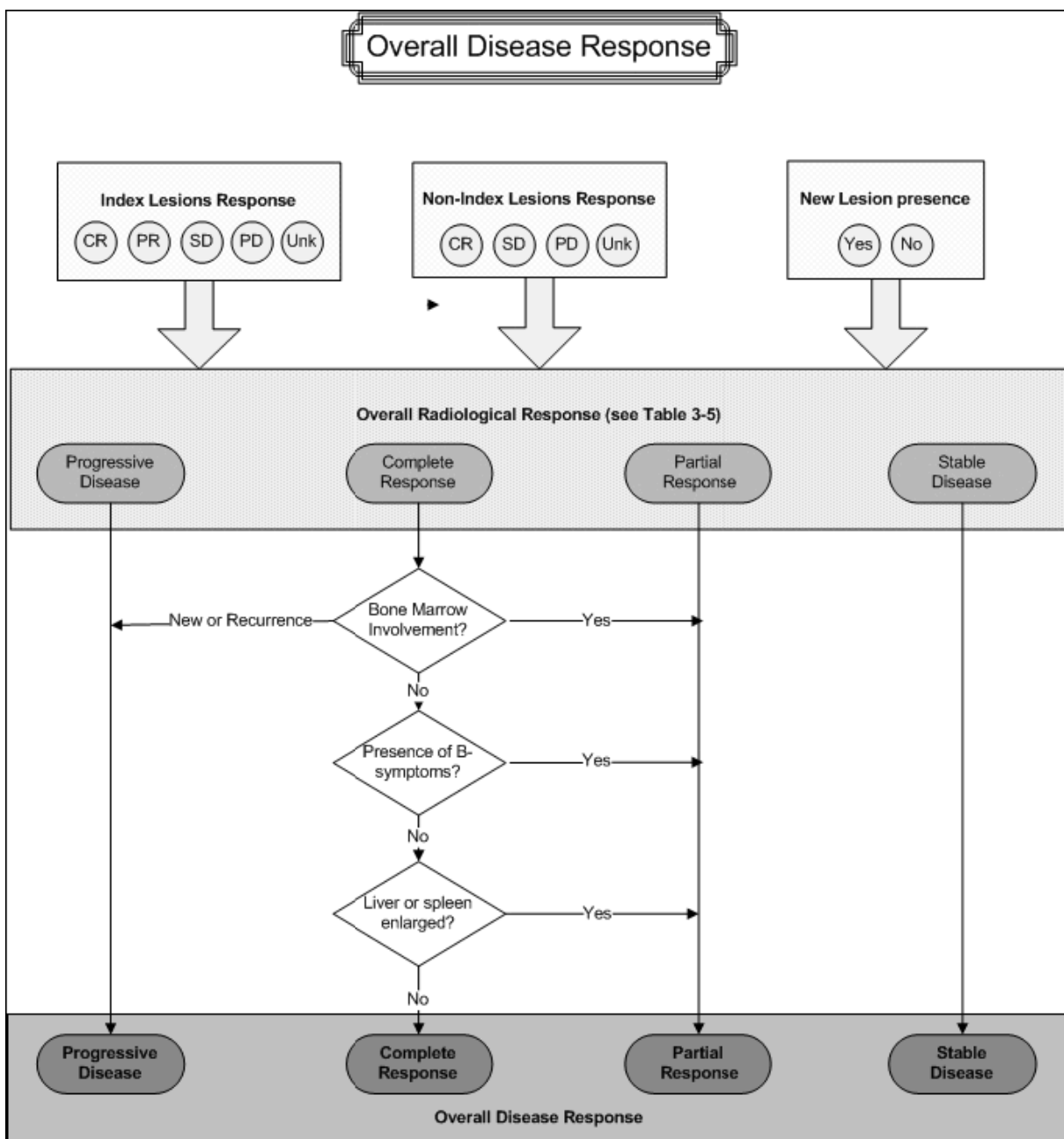
Figure 14-3 **Appendix C - Calculation of the response for non-index lesions**



Notes:

1. In case of a missing status of any of the non-index lesions, the radiological response for non-index lesions at that assessment will be "Unknown (UNK)", unless progression was seen.
2. All lesions must have been measured with the same method as the one used at baseline, otherwise the radiological response for non-index lesions at that assessment will be "Unknown (UNK)".

Figure 14-4 Appendix D - Calculation of the overall disease response



Appendix E - Adaptation for use in maintenance/adjuvant settings

For settings in which no measurable disease is present at baseline (e.g. maintenance), this guideline can be adapted. In such setting, as patients have no more measurable disease at baseline, the event of main interest is no more the Progressive Disease but the Relapsed Disease and the main endpoint is no more the Progression-free survival but the Disease-free survival. The definitions that need to be considered are presented below:

Relapsed Disease

The definition of Relapsed Disease can be derived from the definition of New Lesion (see [Section 14.5.3.4.3](#)) and is as follow:

Appearance of the following will always be considered as **Relapsed Disease (RD)**

- any new nodal lesion > 15 mm in any axis (i.e. previously normal lymph node becoming > 15 mm in any axis) on CT scan or MRI after baseline, or
- any discrete extranodal lesion (including liver or spleen) reliably appearing on CT scan or MRI after baseline, or
- $\geq 50\%$ increase in long axis from baseline of any residual lymph node or mass. A residual lymph node or mass is defined as a previously lymphoma-involved lymph node or mass (>10 mm in short axis (without any upper limit)) that was PET scan negative at baseline and only reliably detected by baseline CT or MRI.

Note: *If a residual lymph node or mass at baseline decreases in size during treatment and becomes normal (i.e. complete disappearance of extranodal mass or ≤ 10 mm in short axis and ≤ 15 mm long axis for nodal mass), then reappearance of an extranodal lesion at the same site or increase of the same nodal mass to > 15 mm in the long axis, will be considered as Relapsed Disease and need to be recorded as a new lesion in the appropriate module of the CRF.*

Disease-Free Survival

Disease-Free Survival (DFS) is the time from date of randomization/ start of treatment to the date of event defined as the first documented relapse of the disease or death due to any cause. If a patient has not had an event, disease-free survival is censored at the date of the last adequate assessment.