Title: Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma After at Least 2 Prior Lines of Chemotherapy

NCT Number: NCT03123393

Protocol Approve Date: 24 April 2018

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
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PROTOCOL

Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma After at Least 2 Prior Lines of Chemotherapy

Sponsor:	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited 40 Landsdowne Street Cambridge, MA 02139 USA Telephone: +1 (617) 679-7000 Please note: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "Sponsor", or "Takeda"
Study Number:	C34004
IND Number:	119,231
EudraCT Number:	2016-003716-12
Compound:	TAK-659
Date:	24 April 2018
Version/Amendment Number:	02

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
27 February 2017	Initial version	Not applicable	Global
14 November 2017	01	Not applicable	Global
24 April 2018	02	Not applicable	Germany-specific

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	European
Serious adverse event and pregnancy reporting	See Sections 10.2, 10.4	See Sections 10.2, 10.4
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

1.3 Protocol Amendment 02 Summary of Changes

This section describes the changes in reference to the Protocol Incorporating Amendment 02.

Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix J. The following is a summary of the major changes made in the amendment:

Changes in Amendment 02

1. The IND number, amendment history, and summary of changes were added to the protocol.
2. The names of the sponsor's signatories were updated.
3. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version was updated from version 4.03 to version 5.0.
4. Definitions of childbearing potential and highly effective contraception methods for female patients of childbearing potential were added to the protocol.
5. Definitions of highly effective contraception methods for male patients who are sexually active with partners of childbearing potential were added to the protocol.
6. A new inclusion criterion was added and the precautions and restrictions section was revised to state that male patients should not donate sperm from the time of signing the informed consent through 180 days after last dose of study drug.
7. One new exclusion criterion was added to exclude patients with known hypersensitivity reactions to the active substance or to any of the excipients of the study drug.
8. Suspected pneumonitis was specifically added to all Grade 3 and Grade 4 nonhematologic toxicities.
9. A urine pregnancy test for all women of childbearing potential was added to the end of treatment visit.
10. Reasons for discontinuation of treatment with study drug were revised.
11. Reasons for withdrawal of patients from the study were revised.
12. Reasons for early discontinuation of the study by the sponsor were added to the protocol.
13. Human immunodeficiency virus (HIV), hepatitis B, and hepatitis C virus tests were added during the Screening period.
14. Fresh tumor biopsy criteria were revised.
15. Optional tumor biopsy criteria were revised.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** TAK-659	
Title of Protocol: Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma After at Least 2 Prior Lines of Chemotherapy	**IND No.:** 119,231	**EudraCT No.:** 2016-003716-12
Study Number: C34004	**Phase:** 2	

Study Design:

This is an open-label, multicenter, phase 2 study to evaluate the efficacy and safety of TAK-659 as a single agent in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior lines of chemotherapy. Eligible patients will also be ineligible for autologous stem cell transplant (ASCT) or be patients for whom ASCT has failed.

This study will start with a lead-in dose exploration phase (Stage 1) during which two TAK-659 dose regimens will be evaluated in two patient cohorts (Cohorts A and B). Patients in Cohort A will receive a daily dose of 100 mg TAK-659 continuously throughout the study. In Cohort B, patients will follow a ramp-up dosing schema leading to a full dose of 100 mg QD TAK-659. Patients will initially receive 60 mg QD TAK-659 for one cycle of 28 days, and if tolerated well, will then receive 80 mg QD TAK-659 for the next cycle, and subsequently 100 mg QD TAK-659 in the 3rd cycle and beyond. At the end of each cycle during the ramp-up, patients will be assessed for their suitability to dose-escalate to the next level based on safety and tolerability.

If the patient experiences any drug-related adverse events that require dose modification (inclusive of dose held and dose reduction) per protocol in a given dose cycle, dose escalation will not proceed to the next level. If the AE(s) resolves, the patient may then restart dose escalation in the next cycle either at the same dose or a reduced dose according to the protocol-defined dose reduction criteria. In case dose reduction is not required, when the patient resumes the study drug at the same dose, dose escalation to the next dose level and further to the full dose of 100 mg QD TAK-659 may be pursued if no recurrence of the same AE(s) or any other AEs leading to dose modification is observed in the next cycle of treatment. However, if the same AE(s) or different AE(s) requiring dose modification occur in two consecutive cycles at the same dose level, further dose escalation is not allowed. If the patient resumes the study drug at a reduced dose per protocol, no dose re-escalation is recommended. Approximately 20 patients are expected to be enrolled into each cohort, with a total of ~40 patients planned for Stage 1.

Upon completion of Stage 1, the dose exploration analysis will occur. Based on the posterior probability of response comparison between the 2 cohorts, one TAK-659 dose regimen will be selected to proceed to Stage 2. During this analysis, if both Stage 1 regimens are determined to be ineffective, termination of the study without proceeding to Stage 2 may be considered. However, other considerations should be taken into account when making this development decision including, but not limited to, sample size, relevant data from other TAK-659 trials, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting.

During the Stage 2 efficacy evaluation phase, it is expected that approximately 82 patients will be enrolled. Once enrolled, patients will be administered TAK-659 orally in 28-day treatment cycles according to the selected dose regimen of TAK-659 from Stage 1. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of study treatment and have at least 1 posttreatment response evaluation, an interim analysis will be performed to assess futility. The study may either stop for futility or continue as planned.

Patients on TAK-659, including those who achieve a complete response (CR), may receive study drug until they experience disease progression or unacceptable toxicities. Patients will be followed for progression-free survival (PFS) (applies only for patients who discontinue study for reasons other than disease progression) and overall survival (OS) after the last dose of study drug.

Sparse pharmacokinetic (PK) samples to support population PK and exposure–response analyses will be collected from all patients, along with blood and tumor tissue samples for biomarker analysis.

The objectives are to evaluate the efficacy of TAK-659 as measured by overall response rate (ORR) and other efficacy variables, including CR rate, ORR at cycles 3, 6 and 9, duration of response (DOR), PFS, and OS, and to determine the safety and tolerability of TAK-659. Disease assessments will be performed by central review of radiology by an independent radiologic review committee (IRC) according to the modified 2007 and 2014 (Lugano) International Working Group (IWG) criteria. ORR by IRC per the 2007 IWG criteria will be used as the primary endpoint for the study.

Primary Objective:

The primary objective is to assess the efficacy of TAK-659 as measured by IRC-assessed ORR in patients with DLBCL (Stage 2).

Key Secondary Objective:

The key secondary objective is to assess CR rate per IRC in patients with DLBCL (Stage 2).

Secondary Objectives:

- To select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1) and assess efficacy using ORR per IRC (Stage 2).
- To assess ORR per IRC at 3, 6, and 9 cycles in patients with DLBCL (Stage 2).
- To assess DOR and duration of CR per IRC in patients with DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with germinal center B-cell (GCB) DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with DLBCL transformed from indolent non-Hodgkin lymphoma (NHL) (Stage 2).
- To assess PFS per IRC in patients with DLBCL (Stage 2).
- To assess OS in patients with DLBCL (Stage 2).

Additional Objectives:

- To assess the safety and tolerability of TAK-659 in the patient population under study (Stages 1 and 2).
- To assess the number of responding patients proceeding to ASCT or allogeneic stem cell transplant (Stage 2).
- To collect TAK-659 plasma concentration–time data to contribute to population PK and exposure–response analyses (Stages 1 and 2).

Exploratory Objectives:

CCI [redacted]

Patient Population: Male or female patients aged 18 years or older with histologically confirmed DLBCL, including de novo disease or transformed disease from indolent NHL. Patients must also be relapsed or refractory to ≥2 prior lines of chemotherapy based on standard of care and may not have failed more than 4 prior lines of therapy. Patients must have either failed or not be eligible for ASCT. Patients must have [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET)–avid disease measurable by computed tomography (CT)/magnetic resonance imaging (MRI), and Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

Number of Patients:	**Number of Sites:**
Approximately 122 patients will be enrolled in the study, including 40 patients (20 per dose schedule) in the lead-in dose exploration phase (Stage 1) and 82 patients in the efficacy evaluation phase (Stage 2).	Approximately 50 sites in North America and Europe

Dose Levels:	**Route of Administration:**
TAK-659: 100 mg QD or a 3-dose-level ramp-up schema leading to 100 mg QD (60, 80, 100 mg QD) in 28-day treatment cycles.	TAK-659: oral
Duration of Treatment: Treatment will continue until disease progression, unacceptable toxicities, or withdrawal for other reasons. The estimated median treatment duration is 6 months.	**Period of Evaluation:** PFS follow-up: every 3 months after the last dose of study drug until progression, the start of alternative therapy, or conclusion of the study, whichever occurs first (for patients who discontinue for reasons other than disease progression). OS follow-up: every 3 months after the last dose of study drug until death or conclusion of the study, whichever occurs first.

Main Criteria for Inclusion:

1. Male or female patients aged 18 years or older.
2. Patients must have histologically confirmed DLBCL, including de novo disease or transformed disease from indolent NHL.
   a. Patients with transformed DLBCL must meet 2016 World Health Organization (WHO) criteria for DLBCL on last biopsy before study entry and have ≥1 prior histological diagnosis of follicular lymphoma (FL) or other indolent disease.
   b. To be enrolled in the study, patients must have a pathologically confirmed diagnosis of one of the following DLBCL subtypes based on the 2016 WHO classification criteria for lymphoid neoplasms:
      i. DLBCL, not otherwise specified (NOS), including GCB and activated B-cell/non-GCB subtypes.
         1) DLBCL with double expression of MYC and BCL-2 and/or BCL-6 protein without gene aberration is eligible under DLBCL, NOS.
         2) High-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 translocations (double-hit DLBCL under DLBCL, NOS, based on the 2008 WHO classification criteria) is not eligible for this study.
      ii. T-cell/histiocyte-rich large B-cell lymphoma.
      iii. DLBCL associated with chronic inflammation.
      iv. Epstein-Barr virus (EBV)+DLBCL, NOS (EBV+DLBCL of the elderly based on the 2008 WHO classification criteria for lymphoma).
      v. FL Grade 3B.
   c. Local pathology review for histological confirmation:
      i. A formalin-fixed, paraffin-embedded tumor block or appropriately stained slides from a fresh biopsy is required. If a fresh specimen cannot be obtained without putting the patient at unjustifiable risk, slides prepared from the archival specimen supporting a prior DLBCL diagnosis may be submitted to local pathology review to fulfill this inclusion criterion.
         ii. If the patient requires immediate treatment and the sample cannot be evaluated by local pathology review before the start of treatment, medical monitor or designee approval for initiation of protocol treatment is required; in this case, submission of an appropriate sample (either fresh biopsy acquired before Cycle 1 Day 1 or archival sample) to local pathology review is absolutely required, and the DLBCL diagnosis should be confirmed no later than 4 weeks after Cycle 1 Day 1.
3. Relapsed or refractory to ≥2 prior lines of chemotherapy based on standard of care that include at least:
   a. The standard first-line chemotherapy regimen containing rituximab and an anthracycline (eg, R-CHOP

[cyclophosphamide+doxorubicin (hydroxydaunomycin)+vincristine (Oncovin)+prednisone with rituximab]) or equivalent if anthracycline is contraindicated; included are DLBCL patients transformed from indolent lymphoma who may have already received R-CHOP or equivalent as part of their indolent lymphoma treatment. Therefore, alternative frontline therapy other than R-CHOP or equivalent used for DLBCL post-transformation may be acceptable upon discussions with the sponsor.

and

b. One additional systemic chemotherapy as a second-line salvage therapy that may have included ASCT.
   i. Included are ASCT-eligible patients who failed ASCT following response to a standard salvage regimen, or who did not respond to salvage therapy and were therefore not indicated for ASCT, or who did not proceed to ASCT after responding to salvage therapy for other reasons, such as insufficient CD34+ cell harvest, and then relapsed.
   ii. Also included are ASCT-ineligible patients who were refractory to or relapsed after a second-line systemic chemotherapy regimen.
   iii. Also included are patients not indicated for systemic chemotherapy regimens who were refractory to or relapsed after an alternative second-line salvage therapy.

4. Patients should not have failed more than 4 prior lines of therapy.
   a. Pre-induction salvage chemotherapy and ASCT should be considered 1 therapy.
   b. Antibody therapy (eg, rituximab) given in combination with or as consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 therapy.
   c. Antibody therapy given as a single agent should be considered 1 therapy.
   d. Prior treatment with single-agent B-cell receptor in-pathway inhibitors such as ibrutinib and idelalisib is permitted and will not count as a prior line of therapy.
   e. For patients with DLBCL transformed from indolent lymphoma, any treatment received for the indolent disease prior to the transformation to DLBCL will, in general, not count towards the 2 to 4 prior lines of therapy required for DLBCL in this study.
5. For patients who have relapsed or progressed after achieving a response (defined as CR or PR), documented, investigator-assessed relapse or progression after the last treatment is required. For patients who are refractory to their last treatment (defined as not having achieved a CR or PR before enrollment by investigator assessment), documented progression will not be required.
6. Must have FDG-PET–avid measurable disease that meets the size criteria per IWG (≥1.5 cm in the longest diameter for a lymph node or nodal mass, or ≥1.0 cm in the longest diameter for extranodal disease) as assessed on cross-sectional imaging by CT/MRI (CT is to be performed with contrast unless contrast is medically contraindicated).
7. ECOG performance status score of 0 or 1.
8. Life expectancy of >3 months.
9. Patients must have adequate organ function, including the following:
   a. Bone marrow reserve: absolute neutrophil count ≥1000/μL, platelet count ≥75,000/μL (≥50,000/μL for patients with bone marrow involvement), and hemoglobin ≥8 g/dL (red blood cell and platelet transfusions allowed ≥14 days before assessment).
   b. Hepatic: total bilirubin ≤1.5 times the upper limit of the normal range (ULN); alanine aminotransferase and aspartate aminotransferase ≤2.5×ULN.
   c. Renal: creatinine clearance ≥60 mL/min either as estimated by the Cockcroft-Gault equation or based on urine collection (12 or 24 hours).
   d. Other:
      i. Lipase ≤1.5×ULN and amylase ≤1.5×ULN with no clinical symptoms suggestive of pancreatitis or cholecystitis.

ii. Blood pressure Grade ≤1 (hypertensive patients are permitted if their blood pressure is controlled to Grade ≤1 by hypertensive medications).
iii. Glycosylated hemoglobin is ≤6.5% (hyperglycemic patients permitted if glucose is well controlled by hypoglycemic medication).

Main Criteria for Exclusion:

1. Central nervous system lymphoma; active brain or leptomeningeal metastases as indicated by positive cytology from lumbar puncture or CT/MRI by local assessment.
2. Known human immunodeficiency virus–related malignancy.
3. Systemic anticancer treatment (including investigational agents) less than 3 weeks before the first dose of study treatment (≤4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or anti-tumor vaccine).
4. Radiotherapy less than 3 weeks before the first dose of study treatment. If prior radiotherapy occurred <4 to 6 weeks before study start, as radiated lesions cannot be reliably assessed by FDG-PET, nonradiated target lesions are required for eligibility, and prior radiotherapy information must be submitted to the IRC.
5. Prior ASCT within 6 months or prior ASCT at any time without full hematopoietic recovery before Cycle 1 Day 1, or allogeneic stem cell transplant any time.
6. Use or consumption of any of the following substances:
   a) Medications or supplements that are known to be inhibitors of P-glycoprotein (P-gp) and/or strong reversible inhibitors of cytochrome P450 (CYP) 3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, use of these agents is not permitted during the study except when an adverse event (AE) must be managed.
   b) Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drug. In general, use of these agents is not permitted during the study except when an AE must be managed.
   c) Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are not permitted during the study.

Main Criteria for Evaluation and Analyses:

- Primary: ORR as assessed by IRC according to modified 2007 IWG criteria for malignant lymphoma.
- Key secondary: CR rate as assessed by IRC according to the modified 2007 IWG criteria.
- Secondary:
  - ORR per IRC according to the 2014 IWG (Lugano) criteria (Stage 2).
  - CR rate per IRC according to the 2014 IWG (Lugano) criteria (Stage 2).
  - ORR per IRC to select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1).
  - ORR per IRC at 3, 6, and 9 cycles, respectively (Stage 2).
  - DOR and duration of CR per IRC (Stage 2).
  - ORR per IRC in patients with GCB DLBCL (Stage 2).
  - ORR per IRC in patients with DLBCL transformed from indolent NHL (Stage 2).
  - PFS per IRC (Stage 2).
  - OS (Stage 2).
- The IRC will evaluate the assessments above using both the modified 2007 IWG criteria for malignant lymphoma and the 2014 IWG (Lugano) criteria. Unless otherwise specified, evaluations using the 2007 IWG criteria will be the primary analyses, and evaluations using the 2014 IWG (Lugano) criteria will be the sensitivity analyses.

- Additional:
  - Percentage of patients who experience AEs, Grade ≥3 AEs, serious AEs, discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range (Stages 1 and 2).
  - Percentage of patients proceeding to ASCT or allogeneic stem cell transplant out of all patients who achieve a best response of PR or CR on study (Stage 2).
  - TAK-659 plasma concentration–time data (Stages 1 and 2).
- Exploratory:

CCI

[redacted]

Statistical Considerations:

For the lead-in dose exploration phase (Stage 1) of the study, assuming a historical control rate of 20% for ORR, at least 20 patients per dosing regimen are required to determine the dosing regimen for the phase 2 efficacy evaluation phase (Stage 2) of the study. Data from both dosing regimens will be analyzed with a Bayesian model assuming prior of Beta(1,1) for each ORR. The dose exploration analysis will occur upon completion of Stage 1 Dosing regimen A will be claimed ineffective if the posterior probability of ORR_A <20% is greater than the threshold of 0.75, likewise for dosing regimen B. If both regimens are deemed to be ineffective, termination of the study without proceeding to stage 2 may be considered. Other considerations for making this decision will be taken into account including, but not limited to, sample size limitation, relevant data from other TAK-659 trials, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting.

If only one dosing regimen is deemed to be ineffective, then the other dosing regimen will be chosen as the dosing regimen for the remaining phase of the study. If neither dosing regimen is claimed to be ineffective, then regimen A will be chosen if the posterior probability of $ORR_A > ORR_B$ is greater than the threshold of 0.55, likewise dosing regimen B will be chosen if the posterior probability of $ORR_B > ORR_A$ is greater than 0.55; if both the posterior probability of $ORR_A > ORR_B$ and the posterior probability of $ORR_B > ORR_A$ are ≤0.55, clinical and safety factors will be considered to choose the dosing regimen for Stage 2.

Consideration of an alternative dose regimen other than the two TAK-659 dose regimens evaluated in Stage 1 is permissible if supported by the Stage 1 data. For example, if the ramp-up dose schema (dose regimen B) is chosen based on the Bayesian model (see above) but majority of patients treated with dose regimen B fail to dose escalate beyond 60 mg QD TAK-659 following the dose escalation criteria, 60 mg QD TAK-659 may be considered as the dose for Stage 2. The Stage 1 data, as well as other relevant supportive data from other trials of TAK-659, will be reviewed and discussed by the Study Steering Committee (SSC). The Stage 2 dose regimen of TAK-659 will be selected based on the recommendation by SSC upon agreement with the sponsor.

For Stage 2, assuming a historical control rate of 20% for ORR and a TAK-659 ORR of 37%, 82 patients are required to detect the improvement in ORR with approximately 91% power using a 1-sided exact binomial test at a significance level of 0.025. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of treatment and have at least 1 posttreatment response evaluated, an interim analysis will be performed. The interim analysis will assess futility, and the study may either stop for futility (if posterior probability of ORR <20% is greater than the threshold of 0.75) or continue as planned.

Sample Size Justification: For the lead-in dose exploration phase (Stage 1), assuming a historical control rate of 20% for ORR, at least 20 patients per dosing regimen are required to determine if either dosing regimen A or dosing regimen B is more effective than the other given a futility threshold of 0.75 and a superiority threshold of 0.55.

For the phase 2 efficacy evaluation phase (Stage 2) of the study, assuming a historical control rate of 20% for ORR and a TAK-659 ORR of 37%, this study will need to enroll at least 82 patients to achieve 91% power at a 1-sided alpha level of 0.025, using an exact binomial test in ORR with approximately 91% power using a 1-sided exact binomial test at a significance level of 0.025.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol and the study medication, expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and, by doing so, agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

ABC	activated B-cell
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC_τ/dose	dose-normalized area under the plasma concentration–time curve during the dosing interval
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CFR	Code of Federal Regulations
CK	creatine kinase
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	United States Food and Drug Administration
FDG-PET	[^{18}F]fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FL	follicular lymphoma

GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HbAc1	glycosylated hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemical; immunohistochemistry
IRB	institutional review board
IRC	independent radiologic review committee
ITAM	immunoreceptor tyrosine-based activating motifs
IV	intravenous; intravenously
IWG	International Working Group
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
NOS	not otherwise specified
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic(s)
PLT	platelets
PO	per os; by mouth (orally)
PR	partial response
PTE	pretreatment events

QD	once daily
QTc	rate-corrected QT interval (msec) of electrocardiograph
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
R-CHOP	cyclophosphamide+doxorubicin (hydroxydaunomycin)+vincristine (Oncovin)+prednisone with rituximab
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SSC	study steering committee
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse events
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Diseases Under Study

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing about 30% of all NHL. It is estimated that approximately 66,000 new cases of NHL, including 20,000 new cases of DLBCL, are diagnosed annually in the United States (US) [1]. DLBCL is a form of aggressive B-cell NHL that is invariably fatal without treatment.

The immunochemotherapy regimen R-CHOP (cyclophosphamide + doxorubicin [hydroxydaunomycin] + vincristine [Oncovin] + prednisone with rituximab) is the standard treatment for patients newly diagnosed with DLBCL. This regimen results in complete remission in approximately 60% to 75% of patients with frontline DLBCL [2,3]. It is considered curative in a subset of patients, with both a reported 5-year progression-free survival [4,5] and an overall survival (OS) of approximately 50%. However, DLBCL is highly heterogeneous in histology, clinical behavior, and underlying biology, and therefore exhibits significant variation in outcome after therapy.

High-dose chemotherapy, including salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), and autologous stem cell transplant (ASCT) are the treatment of choice for patients with relapsed disease. For patients with disease relapse following transplant or for patients not eligible for transplant, there is no clear standard of care; therefore, multiple chemotherapy regimens and investigational agents in clinical trials are being used to treat such patients. Clinically meaningful benefit is rarely achieved, however, in patients with progressive disease (PD) following multiple regimens.

The classification of DLBCL continues to evolve on the basis of emerging clinical, pathologic, molecular, and genetic data. The World Health Organization (WHO) 2016 classification of lymphoid neoplasms [6] recognizes a number of DLBCL subtypes based upon their distinct clinical-pathologic characteristics and their molecular cell of origin classification.

Distinct subtypes of DLBCL recognized under the WHO classification are considered separate entities and include T-cell/histiocyte-rich large B-cell lymphoma, primary DLBCL of the central nervous system (CNS), primary cutaneous DLBCL, leg type, and Epstein-Barr virus (EBV)-positive DLBCL of the elderly. However, the overwhelming majority of cases are classified as DLBCL, not otherwise specified (NOS).

By definition, DLBCL, NOS, is dominated by large atypical cells with vesicular chromatin, discernible nucleoli, and identifiable mitoses [7]. Although partial involvement of nodes can occur and create diagnostic difficulty, the majority of cases demonstrate a diffuse growth pattern. The majority of DLBCL, NOS, can be divided into centroblastic, immunoblastic, and anaplastic variants and (most recently) plasmablastic subtypes primarily on the basis of morphology [7,8]. The morphological distinction between centroblastic and immunoblastic variants is particularly prone to poor interobserver concordance [9], and such subdivision appears to have little prognostic significance [7]; therefore, morphological subclassification of DLBCL is neither emphasized in

the WHO classification nor considered mandatory by most practicing pathologists. In contrast to the limited utility of morphological classification of DLBCL, NOS, immunohistochemical (IHC) classification is considered part of routine care.

The molecular pathogenesis of DLBCL is a complex, multistep process that ultimately results in the transformation and expansion of a malignant clone of germinal or postgerminal B-cell origin. The WHO classification of lymphoid neoplasms describes use of gene expression profiling or IHC to subclassify DLBCL, NOS, into tumors of germinal center B-cell (GCB)-like and nongerminal center (eg, activated B-cell [ABC]-like and primary mediastinal B-cell lymphoma) origin and indicates that these 2 classes of tumor have different prognoses with current therapies [6]. The non-GCB and GCB subtypes occur with approximately equal frequencies [2,10]. GCB DLBCL tumors express many genes found in normal GCBs, while gene expression in ABC DLBCL resembles that of antigen-ABCs. In particular, ABC DLBCL expresses many targets of NF-κB signaling [11]. ABC DLBCL has an inferior clinical outcome compared with GCB DLBCL, with an OS of approximately 40% [12].

There are other classification systems [13] that have a molecular basis, including one proposed by Monti et al [14]. In that categorization system, gene-set enrichment analysis of a large series of DLBCL tumors revealed an increased abundance of specific genes within each of 3 subtypes: oxidative phosphorylation, B-cell receptor (BCR)/proliferation, or host response. The BCR / proliferation subtype has abundant expression of cell-cycle regulatory genes, DNA repair genes, and higher levels of many components of the BCR signaling cascade, including spleen tyrosine kinase (SYK). It is expected that SYK inhibition can target the BCR/proliferation subtype of DLBCL and that a portion of patients in each WHO classification subtype will have tumors that are related to the activation of this pathway.

4.1.2 Study Drug

TAK-659 is a potent and reversible inhibitor of SYK being developed for oncology indications, the pathogenesis of which are either driven by, or significantly contributed to by, SYK-mediated signaling. TAK-659 inhibits SYK-purified enzyme with a concentration producing 50% inhibition (IC_{50}) of 3.2 nM. In cultured human tumor cells, TAK-659 potently inhibited SYK activity in hematopoietic-derived cell lines (Section 4.1.3). In a broad kinase panel, TAK-659 demonstrated a more than 50-fold selectivity for SYK over 290 other protein kinases screened. Subsequent dose-response analysis independently confirmed the potency of TAK-659 on 4 of these enzymes (FLT-3, ZAP-70, JAK3, and vascular endothelial growth factor receptor 2), with potency ranging from 4.6 to 135 nM.

4.1.3 Nonclinical Experience

TAK-659 is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FLT3. SYK is a nonreceptor tyrosine kinase with SH2-binding domains that bind to phosphorylated immunoreceptor tyrosine activation-motifs (ITAMs) located on B and T cells and certain natural killer (NK) cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling cascades that promote cell survival, growth, and proliferation, transcriptional activation, and cytokine release in these cell types. SYK is expressed ubiquitously

in hematopoietic cells, and abnormal function of SYK has been implicated in NHL, including follicular lymphoma (FL), DLBCL, and mantle cell lymphoma (MCL). TAK-659 inhibits SYK-purified enzyme with an IC_{50} of 3.2 nM and a concentration producing half-maximal response ranging from 25 to 400 nM in sensitive cell systems. Nonclinically, TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models, including the OCI-Ly10 model, an ABC-like-DLBCL model; the OCI-Ly19 model, a GCB-DLBCL model; the PHTX-95L model, a primary human DLBCL model; the TMD8 ABC-DLBCL model; the RL FL model; and the MINO MCL model.

4.1.4 Clinical Experience

As of 05 September 2017, 181 patients have been dosed with TAK-659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001 (advanced solid tumors and lymphoma), 32 patients in Study C34002 (R/R AML), 19 patients in Study C34003 (advanced solid tumor), and 9 patients in Study C34005 (advanced NHL). Both the C34001 and C34002 studies are evaluating TAK-659 as a single agent, while the C34003 and C34005 studies are evaluating TAK-659 in combination with nivolumab (C34003) and 5 additional combination agents (C34005). Different data cutoff dates were used to provide the most current clinical information, given that the ongoing studies are in various stages of conduct. The most current safety and efficacy data for Study C34001 are from the 02 June 2017 data cutoff date. The most current safety and efficacy data for Study C34002 are from the 24 May 2017 data cutoff date. In Study C34003, the TAK-659 dose has been evaluated across 3 dose levels of 60 mg, 80 mg, and 100 mg and the maximum tolerated dose (MTD) determination is pending. In Study C34005, TAK-659 is currently being evaluated at 60mg with plans to escalate to 100 mg.

4.1.4.1 Ongoing Studies With TAK-659

As of 05 September 2017, 181 patients have been dosed with TAK-659 in 4 ongoing studies, including 121 patients in the first-in-human (FIH) Study C34001, 32 patients in Study C34002, 19 patients in Study C34003, and 9 patients in Study C34005.

Study C34001: As of 02 June 2017, the TAK-659 dose was escalated from 60 mg to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [90 patients], and 120 mg [7 patients]). The MTD for patients with lymphoma and solid tumors has been determined to be 100 mg once daily (QD). Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 111 patients treated in this study (92 patients with lymphoma, including 5 patients with chronic lymphocytic leukemia [CLL] and 19 patients with solid tumors), 96 patients had discontinued from study by the June 2017 data cutoff date. The reasons for discontinuation included PD (45 patients), adverse events (AEs) (29 patients), symptomatic deterioration (13 patients), initiation of hematopoietic stem cell transplant (2 patients), protocol violation (1 patient), withdrawal by subject (1 patient), and other (5 patients).

Study C34002: As of 24 May 2017, 31 patients had enrolled. TAK-659 has been escalated from 60 mg QD to 160 mg QD, and an additional dose level of 80 mg BID is also being evaluated. The MTD/RP2D has not yet been determined. Of the 31 patients treated in this study, 28 patients had

discontinued from the study as of the May 2017 data cutoff date. The reasons for discontinuation included PD (5 patients), AEs (18 patients), symptomatic deterioration (2 patients), withdrawal by subject (1 patient), and other (2 patients).

The reported AEs were generally as expected on the basis of nonclinical toxicology findings of TAK-659 and the patient population being studied. As of 02 June 2017, the most common treatment-related AEs reported in Study C34001 (≥20% of patients) have been aspartate aminotransferase (AST) increased (49 patients [44%]), amylase increased (39 patients [35%]), lipase increased (31 patients [28%]), alanine aminotransferase (ALT) increased and diarrhea (28 patients each [25%]), blood creatinine phosphokinase (CPK) increased and hypophosphatemia (26 patients each [23%]), and fatigue (22 patients [20%]).

The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (23 patients [21%]), hypophosphatemia (18 patients [16%]), lipase increased (15 patients [14%]), neutropenia (14 patients [13%]), CPK increased (13 patients [12%]), anemia and AST increased (7 patients each [6%]), and pneumonia (5 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase increased, AST and ALT increased, and blood CPK increased. In Study C34001, as of 02 June 2017, there were 35 on-study deaths. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated varicella, and respiratory failure in the presence of *Pneumocystis jiroveci* pneumonia [PJP]; cytomegalovirus [CMV] and aspergillus infection; and right pneumothorax and renal failure).

In Study C34001, as of 02 June 2017, 9 of 48 response-evaluable patients with DLBCL achieved a complete response (CR) and 4 achieved a partial response (PR). Seven of 10 response-evaluable patients with indolent lymphomas responded (1 CR and 6 PRs). Two out of 4 response-evaluable patients with CLL achieved a response (both PR).

In Study C34002, as of 24 May 2017, there were 15 on-study deaths (one drug-related, multiple organ dysfunction syndrome). To date, the safety profile in Study C34002 appears to be similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both peripheral blast and bone marrow blast counts. Three patients have achieved objective response per IWG 2003 criteria (1 CR, 2 CRi) [15] as of the cutoff date.

4.1.4.2. Clinical Pharmacokinetics of TAK-659

Preliminary pharmacokinetic (PK) results are available across the 60 to 120 mg dose range evaluated in the dose-escalation portion of Study C34001. Preliminary plasma PK results are available in 34 patients (17 lymphoma, 17 solid tumor) after single dosing and in 25 patients (14 lymphoma, 11 solid tumor) after repeated QD dosing for 15 days; preliminary urine PK results are available from 19 patients (12 lymphoma, 7 solid tumor).

Among patients with relapsed/refractory lymphoma, TAK-659 exhibited fast absorption after oral administration of an immediate–release tablet formulation (median T_{max} [time of first occurrence

of C_{max} (maximum observed concentration)] of 2 hours on Days 1 and 15 of Cycle 1). Approximate steady-state PK conditions appeared to be achieved by Cycle 1 Day 8 upon comparison of predose (trough) concentrations available during Cycle 1. Geometric mean values of steady-state, dose-normalized area under the plasma concentration–time curve during the dosing interval (AUC_τ/dose) were similar across the 60 to 100 mg dose range, suggesting no obvious deviation from dose proportionality. Moderate variability was observed in AUC_τ/Dose when pooled across the 60 to 120 mg dose range (coefficient of variation of 30% for Day 1 and 50% for Day 15).

Following repeated QD dosing, TAK-659 was characterized by a mean 2.1-fold accumulation. The mean peak-to-trough fluctuation over the steady-state dosing interval was 4.2. The mean terminal disposition half-life is predicted to be between 24 and 48 hours and will be confirmed in the expansion phase of Study C34001.

The mean ratio of TAK-659 renal clearance to apparent oral clearance was 0.34. Although the exact contribution of renal excretion of TAK-659 to systemic clearance is unknown because absolute bioavailability is unknown, the contribution is expected to be at least 34% of systemic clearance. On average, unbound renal clearance (based on creatinine clearance calculated by the Cockcroft-Gault equation) was 3.9-fold higher than estimated glomerular filtration rate, suggesting that active tubular secretion is the major component of renal clearance. Preliminary analyses demonstrated a relationship between creatinine clearance and both TAK-659 renal clearance and apparent oral clearance, suggesting that renal function can affect TAK-659 systemic exposure.

In vitro studies indicated that TAK-659 undergoes metabolism in human liver microsomes and hepatocytes. Cytochrome P450 (CYP) 3A4/5 contributed to the majority (69.1% to 73.0%) of TAK-659 metabolism in human liver microsomes, with relatively minor contributions by CYP2D6 (16.6% to 30.9%) and CYP1A2 (0% to 8.4%). The relative contribution of hepatic metabolism to systemic clearance is currently unknown; however, current in vitro and clinical PK data suggest that both hepatic metabolism and renal excretion contribute to TAK-659 elimination.

Additional details about TAK-659 PK and metabolism are provided in the TAK-659 Investigator's Brochure (IB).

4.1.5 Risks and Benefits

Because TAK-659 has been administered to a total of only 181 patients as of 05 September 2017, it is not currently possible to describe with certainty the potential adverse effects of the compound.

4.1.5.1 Potential Risks From Nonclinical Studies

Potential risks from nonclinical studies in dogs and rats include the following:

- Lymphoid/hematopoietic effects that include lymphoid depletion and myelosuppression, that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased susceptibility to infection, bleeding, and anemia.
- Epithelial effects on the intestinal tract, urinary tract, and lens. Intestinal effects included minimal-to-slight mucosal hemorrhaging. Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis that led to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.
- Reproductive system effects, including decreased spermatozoa and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries.
- Possible mutation of DNA.
- Growth plate thickening and disorganization (not relevant to adults).
- Lymphoid and hematopoietic effects and reproductive system effects are considered important potential risks.

4.1.5.2 Potential Risks From Clinical Studies

Potential risks based on clinical observations include the following:

On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, asymptomatic lipase or amylase elevations are reported commonly (≥10% of patients). Patients in Study C34004 will have frequent monitoring of lipase and amylase as outlined in the Schedule of Events (Appendix A).

Cases of pneumonitis have been reported in clinical studies with BCR pathway kinase inhibitors, including TAK-659, and pneumonitis is considered an important potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

Further details regarding the benefits and risks associated with TAK-659 may be found in the current version of the TAK-659 IB.

4.1.5.3 Drug-Drug Interaction Risk Assessment

No formal PK drug-drug interaction (DDI) studies have been conducted with TAK-659 in humans. In vitro studies indicate that TAK-659 is a substrate of the efflux transporter P-glycoprotein (P-gp) and is metabolized by CYP3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.4%, respectively; therefore, there is a potential risk for TAK-659 PK to be altered by drugs that are CYP3A inhibitors or inducers or P-gp inhibitors or

inducers. Consequently, use of strong CYP3A inhibitors or inducers or P-gp inhibitors or inducers is not permitted during prespecified periods before the first dose of TAK-659. In general, use of these agents is not permitted during the study unless otherwise specified (see Section 8.2.6).

TAK-659 was not a potent reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 in human liver microsomes at concentrations up to 100 μM (IC_{50} values >100 μM) nor was it a time-dependent inhibitor of these same CYPs at concentrations up to 50 μM. In addition, TAK-659 was not an inducer of CYP1A2, 2B6, or 3A activity or messenger ribonucleic acid expression levels in human hepatocytes at concentrations up to 50 μM. Furthermore, TAK-659 was not an inhibitor of the efflux transporters P-gp or breast cancer resistance protein (BCRP) in Caco-2 cells at concentrations up to 100 μM. When these in vitro findings are viewed in context of the C_{max} observed in patients with lymphoma at the single-agent MTD of 100 mg QD, there is low risk for TAK-659 to cause DDIs via induction or inhibition of CYP enzymes, P-gp, or BCRP.

Additional details on DDI risk are included in the TAK-659 IB.

4.2 Rationale for the Proposed Study

TAK-659 is a selective, reversible, and potent inhibitor of SYK. SYK is a nonreceptor kinase with SH2-binding domains that bind to phosphorylated ITAMs. These domains are located in the cytoplasmic tails of key surface receptors located on B cells, T cells, and certain NK cells. SYK functions normally to mediate ITAM signaling in immune cells by coupling activated immunoreceptors to downstream signaling events that mediate diverse cellular responses, including proliferation, differentiation, phagocytosis, and survival. The SYK pathway can become dysregulated to drive the pathophysiology of various immune disorders and oncogenic processes. Abnormal function of SYK has been implicated in several types of hematopoietic malignancies, including CLL, DLBCL, and indolent lymphomas, such as FL and MCL, in which dependency on BCR-mediated signaling is thought to be important to the survival of tumor cells.

Nonclinical evaluation of TAK-659 in multiple mouse DLBCL xenograft models demonstrated significant antitumor activity. These models, including HBL-1 (DLBCL cell line), PHTX-95L (primary DLBCL tumor), and OCI-Ly10 (ABC–like DLBCL cell line), represent genetic heterogeneity underlying the disease. In addition, tumor growth inhibition correlated with markers of SYK pathway modulation in the HBL-1 and PHTX-95L mouse xenograft models. In the FIH study of TAK-659, 4 of 9 heavily pretreated patients with DLBCL achieved objective responses across multiple dose levels of TAK-659 during dose escalation. This study plans to further evaluate TAK-659 in relapsed and refractory DLBCL after 2 prior lines of chemotherapy, which represents an unmet medical need setting in which there is no standard of care available.

4.2.1 Rationale for Dose and Schedule Selection

TAK-659 has been evaluated as a single agent given PO on a continuous daily dosing schedule in its FIH study (C34001) in patients with advanced solid tumors or lymphoma. Four dose levels (60, 80, 100, and 120 mg QD) have been evaluated in the dose-escalation portion of Study C34001, and the MTD has been determined to be 100 mg QD. Following the safety expansion of the 100 mg cohort, Study C34001 is currently in the dose-expansion phase, evaluating the efficacy,

safety, and tolerability of TAK-659 administered at the 100 mg dose level in 5 different cohorts of B-lymphocyte malignancies. Early signs of clinical activity in lymphoma have been demonstrated across all doses evaluated.

In Study C34001, as of 02 June 2017, 9 of 48 response-evaluable patients with DLBCL achieved a complete response (CR), and 4 achieved a partial response (PR). Seven of 10 response-evaluable patients with indolent lymphomas responded (1 CR and 6 PRs). Two of 4 response-evaluable patients with CLL achieved a response (both PRs).

These responses have been observed at doses of 60 (1 CR), 80 (1 PR), 100 (9 CRs and 11 PRs), and 120 mg QD (1 PR). These data suggest that doses in the tolerable dose range of 60 to 100 mg are pharmacologically active. Preliminary data show that TAK-659 exhibits an acceptable PK profile across the 60 to 100 mg dose levels that support continuous QD dosing. On the basis of the available safety and tolerability data, the AEs observed with TAK-659 treatment overall are reversible and manageable. The laboratory abnormalities, such as lipase, amylase, and liver function test elevations, were generally asymptomatic.

Although 100 mg QD TAK-659 has been determined to be the MTD and RP2D for lymphoma in Study C34001, the question whether it is the optimal biological dose is outstanding. While an appreciable level of clinical activity was shown at 100 mg QD (20 CR+PR/65 response-evaluable lymphoma patients), responses to TAK-659 were also observed in patients treated with two lower doses evaluated, 60 mg (1 CR/4 response-evaluable lymphoma patients) and 80 mg (1 PR/2 response-evaluable lymphoma patients) QD, suggesting a therapeutic window of TAK-659 extending from 60 mg to 100 mg QD. Plasma PK exposure of TAK-659 was found to be approximately dose proportional, and higher drug exposure levels were observed at 100 mg QD compared to the lower doses of 60 and 80 mg QD. However, the level of SYK target inhibition achieved at different dose/exposure levels is not understood due to lack of available clinical pharmacodynamic data. Additionally, the degree and the temporal profile of the SYK inhibition required to generate clinical efficacy are not known. Therefore, it is plausible that the optimal biological dose may not be the MTD of 100 mg QD and may fall within the therapeutic range between 60 and 100 mg QD.

By the data cut-off of 02 June 2017, 84 lymphoma patients had been treated with 100 mg QD TAK-659 in study C34001. The incidence of high-grade AEs at 100 mg QD was low and the most frequent AEs were asymptomatic laboratory changes. Therefore, the 100 mg QD dose overall has shown a favorable safety and tolerability profile. The median relative dose intensity for patients receiving 100 mg QD was 94.2% (min, max: 13%, 103%) overall but only 80.8% (min, max: 7%, 100%) for the 1st cycle of study treatment. During the first cycle, although only 6% of patients receiving 100 mg QD experienced AEs that led to a dose reduction, 51% of patients had study dose held due to AEs. The advanced disease stage associated with the study patient population and the aggressive nature of the disease may have contributed to the frequent study drug interruptions during the initial therapy.

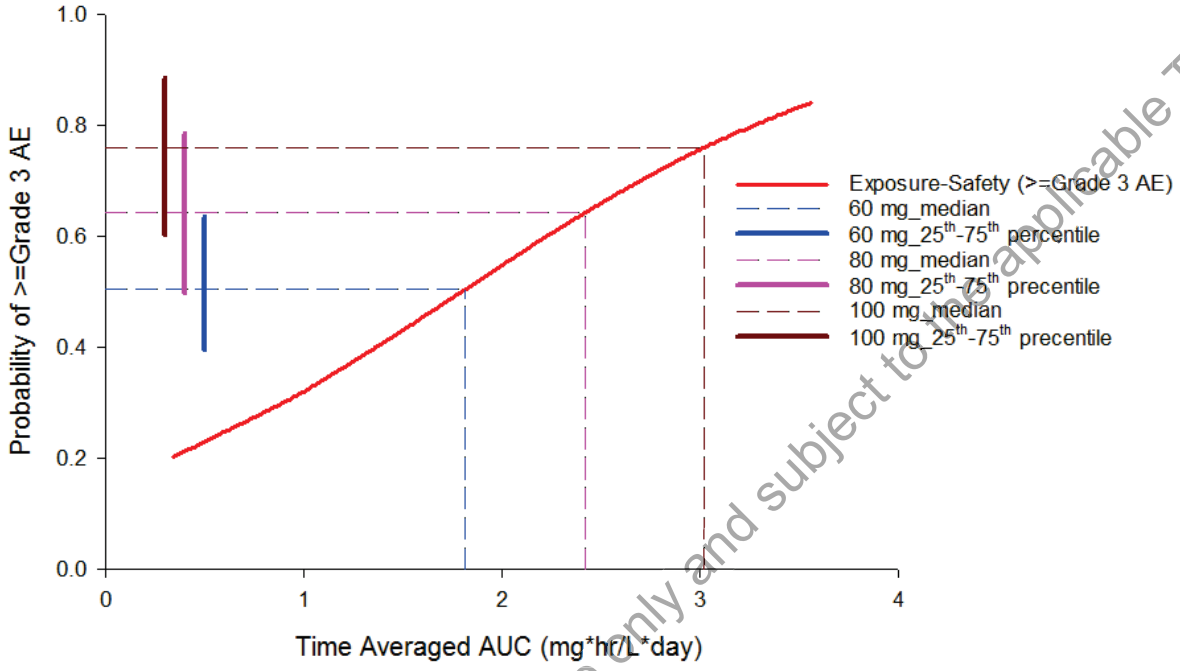
Among the lymphoma responders to TAK-659, the initial response was mostly achieved within the first two cycles of treatment (median time to response 55 days [min, max: 27,168]). Therefore, improved study drug exposure in the initial cycles of treatment may be important for maximizing

the patients' probability of responding to TAK-659. A ramp-up schedule starting from a lower but biologically active dose such as 60 mg QD may alleviate the AE burden for patients and therefore decrease the probability of drug hold and improve relative dose intensity for the first cycle of treatment. Further escalation to 80 mg QD based on the tolerability level and then to the full dose of 100 mg QD allows dose titration for patients so that individual variability in PK and responsiveness to study drug can be better addressed. The evaluation between the 100 mg QD versus a 3-dose ramp-up schema to reach the full dose of 100 mg QD, therefore, is planned in the lead-in phase (Stage 1) of this study. The selection of the dose schedule of TAK-659 for Stage 2 of the study will be based on the efficacy readout, consistent with the purpose of this dose exploration.

Evaluating a ramp-up schema with the potential of dose titration in the lead-in dose exploration portion (Stage 1) was further guided by exploratory exposure-response analyses of the efficacy and safety data from the DLBCL patients in Study C34001. Limited data from a total of 37 DLBCL patients with available PK and efficacy/safety information were included in the analyses. Data were available with the dose range of 60 to 120 mg (N=4, 2, 30 and 1 for 60, 80, 100 and 120 mg groups, respectively). The metric of exposure was the area under the plasma concentration versus time curve per day (derived from individual clearance values on the basis of population PK) for both the exposure/efficacy and exposure/safety analysis.

Logistic regression analysis was performed for efficacy and safety analyses. For efficacy analysis, efficacy data were separated into 2 groups: responders (PR or higher) versus non-responders (SD, PD). Results from the analysis did not show evidence of a relationship between the probability of response (PR or CR) and area under the plasma concentration versus time curve. For the safety analysis, AE data were categorized into 2 groups: Patients with Grade ≥3 AE versus patients with Grade ≤2 AE as their worst grade of AE. Results of the logistic regression suggested a trend between Grade ≥3 AE and exposure (p=0.08) (Figure 4.a). Based on the exposure/safety relationship being observed, probability of having Grade ≥3 AE was estimated for 60 mg, 80 mg and 100 mg using PopPK model simulated steady state exposure (N=1000 for each dose). As shown in Figure 4.a, at the starting dose of 60 mg QD in Cycle 1, which is 60% of the 100 mg QD MTD, the logistic regression model predicted the reduction of the probability of having Grade ≥3 AE from 0.76 to 0.50 when compared to the 100 mg QD dose. While at the dose of 80 mg, the probability of Grade ≥3 AE was reduced from 0.76 to 0.64 when compared to 100 mg QD dose.

Figure 4.a Relationship between TAK-659 exposure (AUCτ) and Grade ≥3 Adverse Event in DLBCL Patients (N=37)



TAK-659 is also being evaluated as a single agent in relapsed/refractory acute myelogenous leukemia in Study C34002, which includes phase 1b dose-escalation and phase 2 dose-expansion phases. Currently, the 60 to 160 mg QD doses of TAK-659 have been determined to be safe and tolerable, and dose escalation is ongoing at the 80 mg BID dose level.

4.2.2 Rationale for PK Assessments

Blood samples for determination of TAK-659 plasma concentrations will be collected during Cycles 1 through 4 via a limited (sparse) sampling strategy to contribute to population PK and exposure–response analyses of TAK-659. [redacted]

Plasma PK data collected in this study may be used individually or in combination with data from other studies to explore the relationship between TAK-659 exposure and clinical safety and efficacy parameters.

4.2.3 Rationale for Biomarker Analysis (Pharmacodynamic Biomarkers and Correlative Studies to Identify Predictive Biomarkers)

SYK is involved in BCR-independent functions, such as B-cell migration and adhesion. To monitor pharmacodynamic effects of TAK-659 in patients with DLBCL, cytokine and chemokine levels at Baseline and posttreatment will be measured as alternative pharmacodynamic endpoints. In addition, changes in the immune cell population in blood will be examined. Changes in

circulating cytokine and chemokine levels and changes in the immune cell profile in each individual patient will be assessed to determine if they are regulated by TAK-659 and/or correlated with clinical response. PK-pharmacodynamic relationships may be evaluated as permitted by the data. Association of the postdose changes of cytokines/chemokines or postdose changes in the immune cell population with clinical response may also be assessed.

Correlative studies will be conducted to identify potential candidate biomarkers (eg, genetic or genomic or gene expression signature) in tumor tissue that are significantly associated with observed clinical response to TAK-659 in patients with DLBCL. These candidate biomarkers include, but are not limited to, BCR-signaling gene expression profiles, cancer-specific somatic gene alterations, DLBCL disease biomarkers relevant to diagnosis and prognosis, and known subtype classifications such as ABC and GCB types. Similar correlative study efforts are ongoing in Study C34001, the FIH study of TAK-659, currently expanding in DLBCL. If any predictive biomarkers are identified in Study C34001, further validation of the biomarkers in relation to clinical response may be conducted in this trial. Initial validation may be a retrospective study, using the clinical efficacy data available for the all-comer population inclusive of both the marker-positive and marker-negative patients. Before the retrospective biomarker validation study, a validation study protocol and a statistical analysis plan (SAP) will be developed with acceptance criteria prespecified for all major parameters under evaluation. If the retrospective validation is successful, the candidate biomarkers may further be prospectively validated in an independent patient population. Ultimately, this may provide a patient-stratification strategy for TAK-659 in the treatment of patients with advanced DLBCL.

4.2.4 Rationale for Pharmacogenomic Assessments

CCI

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective is to assess the efficacy of TAK-659 as measured by independent radiologic review committee (IRC)-assessed ORR in patients with DLBCL (Stage 2).

5.1.2 Key Secondary Objective

The key secondary objective is to assess CR rate per IRC in patients with DLBCL (Stage 2).

5.1.3 Secondary Objectives

The secondary objectives are:

- To select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1) and assess efficacy using ORR per IRC (Stage 2).
- To assess ORR per IRC at 3, 6, and 9 cycles in patients with DLBCL (Stage 2).
- To assess duration of response (DOR) and duration of CR per IRC in patients with DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with GCB DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with DLBCL transformed from indolent non-Hodgkin lymphoma (Stage 2).
- To assess PFS per IRC in patients with DLBCL (Stage 2).
- To assess OS in patients with DLBCL (Stage 2).

5.1.4 Additional Objectives

The additional objectives are:

- To assess the safety and tolerability of TAK-659 in the patient population under study (Stages 1 and 2).
- To assess the number of responding patients proceeding to ASCT or allogeneic stem cell transplant (Stage 2).
- To collect TAK-659 plasma concentration–time data to contribute to population PK and exposure–response analyses (Stages 1 and 2).

5.1.5 Exploratory Objectives

The exploratory objectives are:

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint is ORR as assessed by IRC according to the modified 2007 International Working Group (IWG) criteria for malignant lymphoma [16] (Stage 2).

5.2.2 Key Secondary Endpoint

The key secondary endpoint is CR rate as assessed by IRC according to the modified 2007 IWG criteria [16] (Stage 2).

5.2.3 Secondary Endpoints

The secondary endpoints are:

- ORR per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).
- CR rate per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).
- ORR per IRC to select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1).
- ORR per IRC at 3, 6, and 9 cycles, respectively (Stage 2).
- DOR and duration of CR per IRC (Stage 2).
- ORR per IRC in patients with GCB DLBCL (Stage 2).
- ORR per IRC in patients with DLBCL transformed from indolent NHL (Stage 2).
- PFS per IRC (Stage 2).
- OS (Stage 2).
- The IRC will evaluate the assessments above using both the modified 2007 IWG criteria for malignant lymphoma [16] and the 2014 IWG (Lugano) criteria [15]. Unless otherwise

specified, evaluations using the modified 2007 IWG criteria will be the primary analyses, and evaluations using the 2014 IWG (Lugano) criteria will be the sensitivity analyses.

5.2.4 Additional Endpoints

The additional endpoints are:

- Percentage of patients who experience AEs, Grade ≥3 AEs, serious AEs (SAEs), discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range (Stages 1 and 2).
- Percentage of patients proceeding to ASCT or allogeneic stem cell transplant out of all patients who achieve a best response of PR or CR on study (Stage 2).
- TAK-659 plasma concentration–time data (Stages 1 and 2).

5.2.5 Exploratory Endpoints

The exploratory endpoints are:

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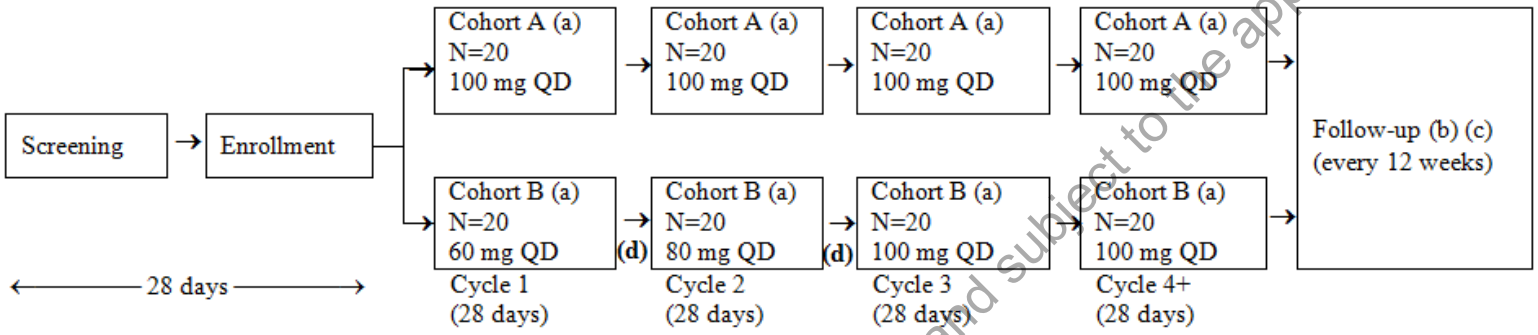
6.0 STUDY DESIGN

6.1 Overview of Study Design

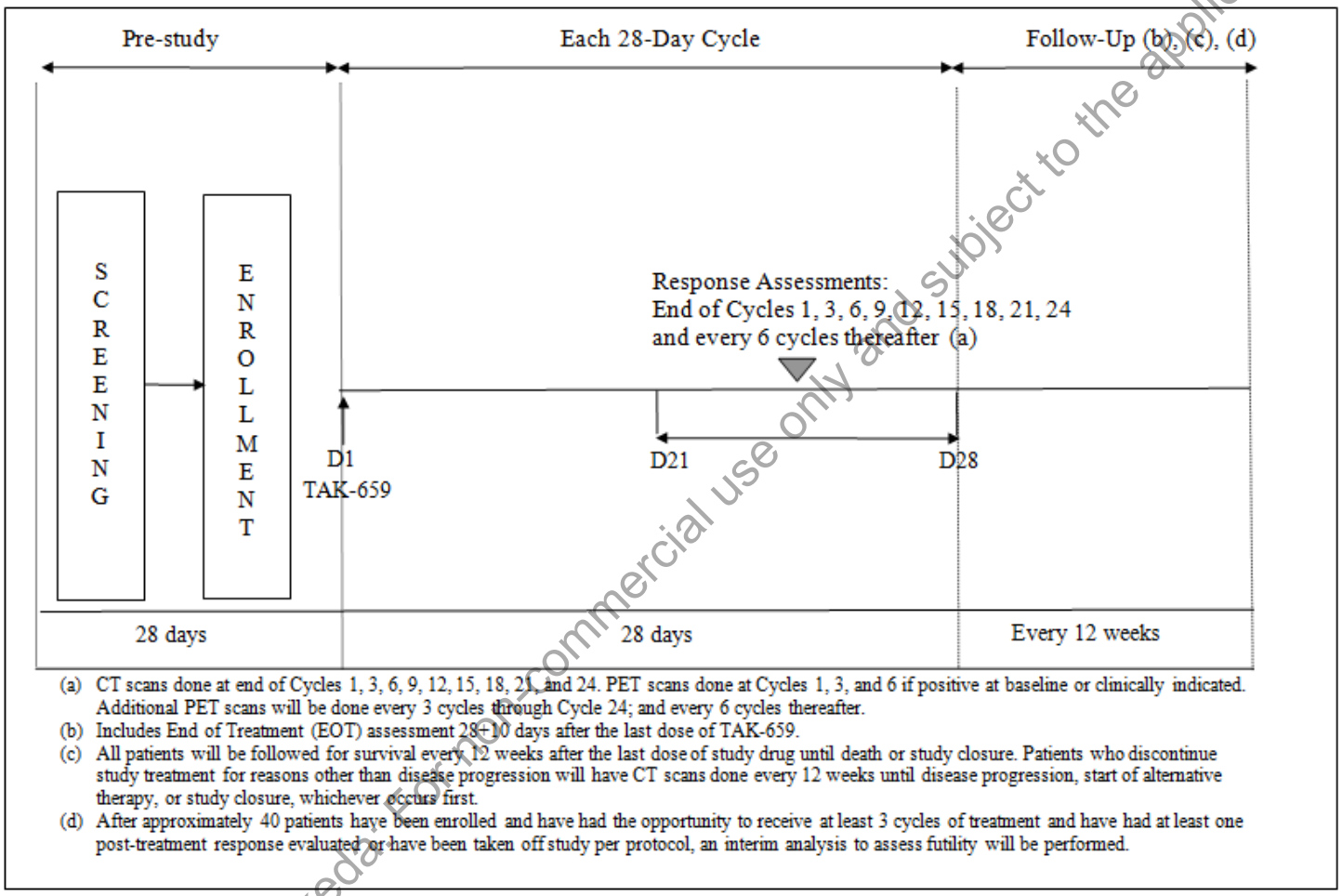
This is an open-label, multicenter, phase 2 study to evaluate the efficacy and safety of TAK-659 as a single agent in patients with relapsed or refractory DLBCL after at least 2 prior lines of chemotherapy. Eligible patients will also be ineligible for ASCT or be patients for whom ASCT has failed. Approximately 122 patients will be treated in the study. This study will include a lead-in dose exploration phase (Stage 1) for dose optimization that is further described below. Study schemas are provided in Figure 6.a and Figure 6.b. See Appendix A for the Schedule of Events.

Figure 6.a Stage 1 Study Schema



(a) CT scans done at end of Cycles 1, 3, 6, 9, 12, 15, 18, 21, and 24. PET scans done at Cycles 1, 3, and 6 if positive at baseline or clinically indicated. Additional PET scans will be done every 3 cycles through Cycle 24; and every 6 cycles thereafter.
(b) Includes End of Treatment (EOT) assessment 28+10 days after the last dose of TAK-659.
(c) All patients will be followed for survival every 12 weeks after the last dose of study drug until death or study closure. Patients who discontinue study treatment for reasons other than disease progression will have CT scans done every 12 weeks until disease progression, start of alternative therapy, or study closure, whichever occurs first.
(d) Patients can proceed to next dose if tolerated. See Section 8.2.6 for dose escalation criteria during Stage 1.

Figure 6.b Stage 2 Study Schema



(a) CT scans done at end of Cycles 1, 3, 6, 9, 12, 15, 18, 21, and 24. PET scans done at Cycles 1, 3, and 6 if positive at baseline or clinically indicated. Additional PET scans will be done every 3 cycles through Cycle 24; and every 6 cycles thereafter.
(b) Includes End of Treatment (EOT) assessment 28+10 days after the last dose of TAK-659.
(c) All patients will be followed for survival every 12 weeks after the last dose of study drug until death or study closure. Patients who discontinue study treatment for reasons other than disease progression will have CT scans done every 12 weeks until disease progression, start of alternative therapy, or study closure, whichever occurs first.
(d) After approximately 40 patients have been enrolled and have had the opportunity to receive at least 3 cycles of treatment and have had at least one post-treatment response evaluated or have been taken off study per protocol, an interim analysis to assess futility will be performed.

This study will start with a lead-in dose exploration phase (Stage 1) during which two TAK-659 dose regimens will be evaluated in two patient cohorts (Cohorts A and B). Patients in Cohort A will receive a daily dose of 100 mg TAK-659 continuously throughout the study. In Cohort B, patients will follow a ramp-up dosing schema leading to a full dose of 100 mg QD TAK-659. Patients will initially receive 60 mg QD TAK-659 for one cycle of 28 days, and if tolerated well, will then receive 80 mg QD TAK-659 for the next cycle, and subsequently 100 mg QD TAK-659 in the 3rd cycle and beyond. At the end of each cycle during the ramp-up, patients will be assessed for their suitability to dose-escalate to the next level based on safety and tolerability.

If the patient experiences any drug-related adverse events that require dose modification (inclusive of dose held and dose reduction) per protocol in a given dose cycle, dose escalation will not proceed to the next level. If the AE(s) resolves, the patient may then restart dose escalation in the next cycle either at the same dose or a reduced dose according to the protocol-defined dose reduction criteria (Section 8.2). In case dose reduction is not required, when the patient resumes the study drug at the same dose, dose escalation to the next dose level and further to the full dose of 100 mg QD TAK-659 may be pursued if no recurrence of the same AE(s) or any other AEs leading to dose modification is observed in the next cycle of treatment. However, if the same AE(s) or different AE(s) requiring dose modification occur in two consecutive cycles at the same dose level, further dose escalation is not allowed. If the patient resumes the study drug at a reduced dose per protocol, no dose re-escalation is recommended. Approximately 20 patients are expected to be enrolled into each cohort, with a total of ~40 patients planned for Stage 1. Details around cohort assignment will be described in the Study Manual.

Upon completion of Stage 1, a dose exploration analysis will occur. Based on the posterior probability of response comparison between the 2 cohorts, one TAK-659 dose regimen will be selected to proceed to Stage 2. During this analysis, if both Stage 1 regimens are deemed to be ineffective, termination of the study without proceeding to Stage 2 may be considered. Other considerations for making this decision should be taken into account including, but not limited to, sample size limitations, relevant data from other TAK-659 studies, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting. Otherwise, one of the two TAK-659 regimens will be selected to proceed to Stage 2.

During the Stage 2 efficacy evaluation phase, it is expected that approximately 82 patients will be enrolled. Once enrolled, patients will be administered TAK-659 orally in 28-day treatment cycles according to the selected dose regimen of TAK-659 from Stage 1. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of study treatment and have at least 1 posttreatment response evaluation, an interim analysis will be performed to assess futility. The study may either stop for futility or continue as planned.

In Stage 2, patients will be administered TAK-659 orally according to the dose regimen selected in Stage 1. Efficacy will be assessed using the IWG revised response criteria for malignant lymphoma (the modified 2007 IWG criteria [16] and the 2014 [Lugano] criteria [15]). Dedicated computed tomography (CT) scans (chest, neck, abdomen, and pelvis) will be performed at Baseline; at the end of Cycles 1, 3, and 6; every 3 cycles up to 24 cycles; and every 6 cycles thereafter. [^{18}F]Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans will be

performed at baseline and at the end of Cycles 1, 3, and 6 if positive at baseline, or when clinically indicated during the study (see Appendix A Schedule of Events). The primary endpoint of this study is ORR, defined as the proportion of patients with CR or PR as determined by independent central review of radiology by an IRC according to the modified 2007 IWG criteria.

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-659. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective date 27 November 2017 [17].

Patients on TAK-659, including those who achieve a CR, may receive study drug until they experience PD or unacceptable toxicities. Patients who discontinue study for reasons other than PD will be followed for PFS every 3 months after the last dose of study drug until PD, the start of alternative therapy, or conclusion of the study, whichever occurs first. All patients, after the last dose of study drug, will be followed for OS every 3 months until death or conclusion of the study, whichever occurs first.

Patients may discontinue therapy at any time. Patients will attend the End-of-Treatment (EOT) visit 28 days (+10) after receiving their last dose of TAK-659 or before the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs.

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6.2 Number of Patients

Approximately 122 patients will be enrolled in the study, including 40 patients (20 per dose schedule) in the lead-in dose exploration phase (Stage 1) and 82 patients in the efficacy evaluation phase (Stage 2) of the study from approximately 50 study centers in North America and Europe. Enrollment is defined as the time of the initiation of the first dose of study drug.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve a clinical response, may receive study drug until they experience PD. Patients will discontinue treatment if they have an unacceptable study drug–related or possibly related toxicity or withdraw for other reasons.

Patients will be followed for 28 days (+10) after the last dose of study drug or until the start of subsequent anticancer therapy (whichever occurs first) to permit the detection of any delayed treatment-related AEs.

PFS follow-up every 3 months after the last dose of study drug or until PD, the start of alternative therapy, or conclusion of the study, whichever occurs first (for patients who discontinue for reasons other than PD) and OS follow-up every 3 months from the last dose of study drug until death or conclusion of study, whichever occurs first, are planned. The primary analysis of the efficacy endpoint will be conducted when the last patient has had the opportunity to receive at least 6 cycles of treatment.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The primary analysis for the efficacy and safety endpoints and authoring of a clinical study report (CSR) may be conducted after all patients enrolled in the study have had the opportunity to complete 6 cycles of treatment with study drug. PFS follow-up every 3 months after the last dose of study drug until PD, the start of alternative therapy, or conclusion of the study, whichever occurs first (for patients who discontinue for reasons other than PD) and OS follow-up every 3 months from the last dose of study drug until death or conclusion of the study, are planned. The estimated time frame for study completion is approximately 41 months. A CSR addendum will be provided to describe additional data collected.

Conclusion of the study will be considered when OS events have occurred in 70% of patients, or 24 months after last patient in, whichever occurs earlier. Alternatively, at the time of the interim analysis, if the prespecified futility boundary is passed, the study will stop; otherwise, the study will continue as planned. The study may be prematurely terminated if, in the opinion of the sponsor, there is sufficient reasonable cause.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame (a)
Primary:		
• ORR as assessed by IRC according to the modified 2007 IWG criteria for malignant lymphoma [16] (Stage 2).	ORR as assessed by IRC.	Up to 12 months.
Key Secondary		
• CR rate as assessed by IRC according to the modified 2007 IWG criteria [16] (Stage 2).	Rate of CR as assessed by IRC.	Up to 12 months.
Secondary:		
• ORR per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).	Rate of ORR as assessed by IRC.	Up to 12 months.
• CR rate per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).	Rate of CR as assessed by IRC.	Up to 12 months.
• ORR per IRC to select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1).	ORR as assessed by IRC.	Up to 12 months.
• ORR per IRC at 3, 6, and 9 cycles (Stage 2).	ORR as assessed by IRC at 3, 6, and 9 cycles, respectively.	Up to 12 months.
• DOR and duration of CR per IRC (Stage 2).	DOR and duration of CR per IRC.	Up to 12 months.
• ORR per IRC in patients with GCB DLBCL (Stage 2).	Rate of ORR as assessed by IRC in a subset of patients.	Up to 12 months.
• ORR per IRC in patients with DLBCL transformed from indolent NHL (Stage 2).	Rate of ORR as assessed by IRC in a subset of patients.	Up to 12 months.
• PFS per IRC (Stage 2).	PFS as assessed by IRC.	Up to 18 months.
• OS (Stage 2).	OS.	Up to 24 months.

IRC= independent radiologic review committee; PFS=progression-free survival; ORR=overall response rate.
(a) Time to last assessment for that endpoint for an individual patient.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 41 months. This includes approximately 23 months of enrollment, estimated median treatment duration of 6 months of treatment, and OS follow-up after last dose of study drug.

7.0 STUDY POPULATION

Patients must have histologically confirmed DLBCL, including de novo disease or transformed disease from indolent NHL. Patients must also be relapsed or refractory to ≥2 prior lines of chemotherapy based on standard of care and may not have failed more than 4 prior lines of therapy. Patients must have either failed or not be eligible for ASCT. Patients must have FDG-PET–avid disease that measurable by CT/magnetic resonance imaging (MRI), and Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male or female patients aged 18 years or older.
2. Patients must have histologically confirmed DLBCL, including de novo disease or transformed disease from indolent NHL.
   a. Patients with transformed DLBCL must meet 2016 WHO criteria for DLBCL [6] on last biopsy before study entry and have ≥1 prior histological diagnosis of FL or other indolent disease.
   b. To be enrolled in the study, patients must have a pathologically confirmed diagnosis of one of the following DLBCL subtypes based on the 2016 WHO classification criteria for lymphoid neoplasms [6]:
      i. DLBCL, NOS, including GCB and ABC/non-GCB subtypes.
         1) DLBCL with double expression of MYC and BCL-2 and/or BCL-6 protein without gene aberration is eligible under DLBCL, NOS.
         2) High-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 translocations (double-hit DLBCL under DLBCL, NOS, based on the 2008 WHO classification criteria) is not eligible for this study.
      ii. T-cell/histiocyte-rich large B-cell lymphoma.
      iii. DLBCL associated with chronic inflammation.
      iv. EBV+DLBCL, NOS (EBV+DLBCL of the elderly based on the 2008 WHO classification criteria for lymphoma) [18].
      v. FL Grade 3B.
   c. Local pathology review for histological confirmation:
      i. A formalin-fixed, paraffin-embedded (FFPE) tumor block or appropriately stained slides from a fresh biopsy is required. If a fresh specimen cannot be obtained without putting the patient at unjustifiable risk, slides prepared from the archival specimen supporting a prior DLBCL diagnosis may be submitted to local pathology review to fulfill this inclusion criterion.

ii. If the patient requires immediate treatment and the sample cannot be evaluated by local pathology review before the start of treatment, medical monitor or designee approval for initiation of protocol treatment is required; in this case, submission of an appropriate sample (either fresh biopsy acquired before Cycle 1 Day 1 or archival sample) to local pathology review is absolutely required, and the DLBCL diagnosis should be confirmed no later than 4 weeks after Cycle 1 Day 1.

3. Relapsed or refractory to ≥2 prior lines of chemotherapy based on standard of care that include at least:
   a. The standard first-line chemotherapy regimen containing rituximab and an anthracycline (eg, R-CHOP) or equivalent if anthracycline is contraindicated; included are DLBCL patients transformed from indolent lymphoma who may have already received R-CHOP or equivalent as part of their indolent lymphoma treatment. Therefore, alternative frontline therapy other than R-CHOP or equivalent used for DLBCL post-transformation may be acceptable upon discussion with the sponsor.

      and

   b. One additional systemic chemotherapy as a second-line salvage therapy that may have included ASCT.
      i. Included are ASCT-eligible patients who failed ASCT following response to a standard salvage regimen, or who did not respond to salvage therapy and were therefore not indicated for ASCT, or who did not proceed to ASCT after responding to salvage therapy for other reasons, such as insufficient CD34+ cell harvest, and then relapsed.
      ii. Also included are ASCT-ineligible patients who were refractory to or relapsed after a second-line systemic chemotherapy regimen.
      iii. Also included are patients not indicated for systemic chemotherapy regimens who were refractory to or relapsed after an alternative second-line salvage therapy.
4. Patients should not have failed more than 4 prior lines of therapy.
   a. Pre-induction salvage chemotherapy and ASCT should be considered 1 therapy.
   b. Antibody therapy (eg, rituximab) given in combination with or as consolidation/maintenance therapy after a chemotherapy regimen (without intervening relapse) should be considered 1 therapy.
   c. Antibody therapy given as a single agent should be considered 1 therapy.
   d. Prior treatment with single-agent BCR in-pathway inhibitors such as ibrutinib and idelalisib is permitted and will not count as a prior line of therapy.
   e. For patients with DLBCL transformed from indolent lymphoma, any treatment received for the indolent disease prior to the transformation to DLBCL will, in general, not count towards the 2 to 4 prior lines of therapy required for DLBCL in this study.
5. For patients who have relapsed or progressed after achieving a response (defined as CR or PR), documented, investigator-assessed relapse or progression after the last treatment is required. For patients who are refractory to their last treatment (defined as not having achieved a CR or

PR before enrollment by investigator assessment), documented progression will not be required.

6. Must have FDG-PET–avid measurable disease that meets the size criteria per IWG (≥1.5 cm in the longest diameter for a lymph node or nodal mass, or ≥1.0 cm in the longest diameter for extranodal disease) as assessed on cross-sectional imaging by CT/MRI (CT is to be performed with contrast unless contrast is medically contraindicated).
7. ECOG performance status score of 0 or 1 (refer to Appendix E).
8. Life expectancy of >3 months.
9. Patients must have adequate organ function, including the following:
    a. Bone marrow reserve: absolute neutrophil count (ANC) ≥1000/μL, platelet count ≥75,000/μL (≥50,000/μL for patients with bone marrow involvement), and hemoglobin ≥8 g/dL (red blood cell [RBC] and platelet transfusion allowed ≥14 days before assessment).
    b. Hepatic: total bilirubin ≤1.5 times the upper limit of the normal range (ULN); ALT and AST ≤2.5×ULN.
    c. Renal: creatinine clearance ≥60 mL/min either as estimated by the Cockcroft-Gault equation (refer to Appendix F) or based on urine collection (12 or 24 hours).
    d. Others:
        - Lipase ≤1.5×ULN and amylase ≤1.5×ULN with no clinical symptoms suggestive of pancreatitis or cholecystitis.
        - Blood pressure Grade ≤1 (hypertensive patients are permitted if their blood pressure is controlled to Grade ≤1 by hypertensive medications).
        - Glycosylated hemoglobin is ≤6.5% (hyperglycemic patients permitted if glucose is well controlled by hypoglycemic medication).
10. Female patients of childbearing potential must:
    a. Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the signing the informed consent form (ICF) through 180 days after the last dose of study drug, OR
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

    Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy, or not being postmenopausal for at least 1 year before screening visit (≥12 months of amenorrhea in the absence of other biological or physiological causes).

11. Male patients, even if surgically sterilized (ie, status postvasectomy), who are sexually active with partners who are of childbearing potential, must:
    a. Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time from the time of signing the informed consent form (ICF) through 180 days after the last dose of study drug, OR
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
12. Male patients should not donate sperm from the time of signing the ICF through 180 days after the last dose of study drug.
13. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
14. Recovered (ie, Grade ≤1 toxicity) from the reversible effects of prior anticancer therapy.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Central nervous system (CNS) lymphoma; active brain or leptomeningeal metastases, as indicated by positive cytology from lumbar puncture or CT/MRI by local assessment.
2. Known human immunodeficiency virus (HIV)–related malignancy.
3. Any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
4. Known hypersensitivity reactions to the active substance or to any of the excipients of the study drug.
5. Life-threatening illness unrelated to cancer that could, in the investigator's opinion, make the patient not appropriate for this study.
6. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before the first dose of the study drug.
7. Systemic anticancer treatment (including investigational agents) less than 3 weeks before the first dose of study treatment (≤4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine).
8. Radiotherapy less than 3 weeks before the first dose of study treatment. If prior radiotherapy occurred <4 to 6 weeks before study start, as radiated lesions cannot be reliably assessed by

FDG-PET, nonradiated target lesions are required for eligibility, and prior radiotherapy information must be submitted to the IRC.

9. Known HIV positive (testing not required).
10. Known hepatitis B surface antigen positive or known or suspected active hepatitis C infection.
11. Prior ASCT within 6 months or prior ASCT at any time without full hematopoietic recovery before Cycle 1 Day 1, or allogeneic stem cell transplant any time.
12. Any clinically significant comorbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active CNS disease, active infection, or any other condition that could, in the opinion of the investigator, compromise the patient's participation in the study.
13. Patients with any of the following cardiovascular conditions are excluded:
    a. Acute myocardial infarction within 6 months before starting study drug.
    b. Current or history of New York Heart Association Class III or IV heart failure (Appendix H).
    c. Evidence of current, uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
    d. Fridericia's corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the Screening period.
    e. Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that, in the opinion of the investigator, are considered to be clinically significant.
14. Major surgery within 14 days before the first dose of study drug or incomplete recovery from any complications from surgery.
15. Systemic infection requiring parenteral antibiotic therapy or other serious infection (bacterial, fungal, or viral) within 21 days before the first dose of study drug. Patients who are at substantial risk of developing an infection may receive prophylaxis at the start of study treatment per investigator's discretion (see Section 8.5.1).
16. Treatment with high-dose corticosteroids for anticancer purposes within 7 days before the first dose of TAK-659. Daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.
17. Patients with another malignancy within 2 years of study start. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.
18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-659 including difficulty swallowing tablets; diarrhea Grade >1 despite supportive therapy.

19. Lack of suitable venous access for the study-required blood sampling for TAK-659.
20. Use or consumption of any of the following substances:
    a. Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, use of these agents is not permitted during the study except when an AE must be managed (see Section 8.5 for details). See Appendix I for a nonexhaustive list of strong CYP3A reversible inhibitors and P-gp inhibitors based on the US Food and Drug Administration (FDA) draft guidance for DDI studies ("Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and labeling Recommendations", February 2012).
    b. Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days or within 5 times the inhibitor or inducer half-life (whichever is longer) before the first dose of study drug. In general, use of these agents is not permitted during the study except when an AE must be managed (see Section 8.5 for details). See Appendix I for a nonexhaustive list of strong CYP3A mechanism-based inhibitors and strong CYP3A inducers and P-gp inducers based on the US FDA draft guidance for DDI studies.
    c. Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are not permitted during the study.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

TAK-659 will be dosed PO, QD, in 28-day cycles. The study drug should be taken on an empty stomach, at least 1 hour before and no sooner than 2 hours after ingestion of food and/or beverages other than water. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed dose. Patients should swallow the study medication whole. The study medication should not be chewed, crushed, or manipulated in any way before swallowing. Administration of the tablets will be guided by the dosing tables provided in the Pharmacy Manual.

Patients should be instructed to take their study medication at approximately the same time each day and not to take more than the prescribed dose at any time. On clinic visit days, patients should be instructed to hold their dose until predose assessments have been performed in the clinic, with the exception of the Cycle 1 Day 8 visit: For this visit, patients should be instructed to take their TAK-659 dose at home before their clinic visit. The reason for this exception is to ensure a range of postdose PK sampling times across the study population for purposes of population PK analyses. If a patient fails to take the TAK-659 dose at the scheduled dosing time (±6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments on that day or subsequent days to account for the missed dose, for example, by taking a double dose of TAK-659 on the following day. Patients should record any skipped doses in their dosing diary (see Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after study medication ingestion, patients should not re-dose following emesis and should record the time of the emesis in their dosing diary (see Study Manual). Patients should resume dosing at the next scheduled time with the prescribed dosage.

8.2 Dose Modification Guidelines

8.2.1 General Principles

Treatment cycles with TAK-659 will occur in 28-day increments. Patients will be evaluated weekly during Cycle 1, every other week during Cycles 2 and 3, and then every cycle thereafter for possible toxicities that may have occurred after previous doses. Toxicities are to be assessed according to the NCI CTCAE, version 5.0. All toxicities that occur during the study will be actively managed following the standard of care unless otherwise specified in the protocol. Patients experiencing AEs attributed to TAK-659 may continue study treatment and maintain the same dose, or have doses of TAK-659 held or modified, or permanently discontinue from the study. Detailed dose-modification guidelines are provided in Section 8.2.4 and 8.2.5. Patients who have the TAK-659 dose held because of a treatment-related or possibly related AE may resume study

drug after resolution of the AE, either at the same dose level or at a dose of TAK-659 reduced (dose reduction) by at least 1 dose level. When a dose reduction occurs, the TAK-659 dose will be reduced to the -1 dose level (see Table 8.a).

If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 can be further reduced if the treating physician decides that the patient is benefiting from study treatment and may benefit at a further-reduced dose of TAK-659 (-2 dose level in Table 8.a). If TAK-659 dosing is delayed for >21 days for TAK-659-related or possibly related toxicities despite supportive treatment per standard clinical practice, or if more than 2 dose reductions are required in a patient, the patient should have study treatment discontinued, unless the treating physician decides that the patient may benefit from continued study treatment after resolution of AEs to Grade ≤1 or to baseline values. In this case, consultation with the medical monitor or designee is required. Under the latter circumstances, dose reduction to a level below 60 mg QD is not advised; therefore, if a patient treated at 60 mg QD experiences AEs that require further dose reduction per guidance below (Table 8.b, Table 8.c), the treating investigator may allow the patient to continue on study if, in the investigator's opinion, the patient may be able tolerate the rechallenge of 60 mg after a period of study drug interruption, provided the benefit–risk assessment is favorable.

The study drug interruption before resolution of AEs to Grade ≤1 or baseline values may be longer than 21 days if justified. In such cases, agreement with the medical monitor or designee must be documented. Patients who discontinue the study for any reason other than death will continue to be followed for AEs for 28 days after the last administration of TAK-659 or until the start of subsequent anticancer therapy, whichever occurs first.

Table 8.a Dose Reduction Levels for TAK-659

Dose Reduction Levels	Dose (Unit)
Planned dose	100 mg
-1 dose level	80 mg
-2 dose levels	60 mg

For AEs that occur during the study but are not related or possibly related to TAK-659, TAK-659 dose modification, in principle, is not required. However, on the basis of medical conditions and the possibility of potential worsening of toxicities from continuous administration of TAK-659, investigators can decide to have the TAK-659 dose held until the resolution of the AEs to a level that is considered clinically appropriate to resume the study drug (nonhematologic AEs with the exception of asymptomatic laboratory changes must be Grade ≤2). In these instances, the study drug will, in general, be resumed at the same dose.

Patients with study drug-related or possibly related Grade 4 nonhematologic toxicities (with the exception of asymptomatic laboratory abnormalities as described in Section 8.2.5) or Grade 4 anemia will, in general, require that treatment with TAK-659 be permanently discontinued (see Section 9.7 for reasons for discontinuation). The patient will be followed until resolution or stabilization of the event. If, in the opinion of the investigator and the sponsor (medical monitor or designee), it is in the patient's best interest to continue treatment with TAK-659, then the dose of

TAK-659 will be reduced by at least 1 dose level when treatment resumes after recovery from the toxicity or toxicities in question to Grade ≤1 or to baseline values. This discussion will be documented in the study file.

Asymptomatic laboratory changes (eg, elevations in serum lipase, amylase, AST, ALT, and CPK) have been observed in patients treated with TAK-659. Although their clinical significance needs to be further evaluated, on the basis of the available data, these laboratory abnormalities related to TAK-659 treatment are, in general, reversible and not associated with evidence of pathological tissue injury. Specific dose modification guidelines relating to asymptomatic laboratory abnormalities are described in detail below. In addition, serum lactate dehydrogenase (LDH) elevation has been observed in most of the patients exposed to TAK-659. Although LDH is monitored during the study, no clinical consequence has thus far been identified with TAK-659–induced LDH elevation; therefore, no TAK-659 dose modification is recommended for LDH.

Dose modification guidelines should be closely followed to manage toxicities during the study; however, on the basis of evolving safety data for TAK-659 and/or individual patient cases, alternative dose modifications may be recommended after discussion between the investigator and the sponsor to maximize exposure of study treatment while protecting patient safety. Discussion and agreement will be documented. The study steering committee (SSC) may be consulted per the SSC charter (see Section 11.2).

8.2.2 Intrapatient Dose Re-escalation

When a dose reduction of TAK-659 is required because of toxicity, dose re-escalation is not advised; however, dose re-escalation may be allowed if, following an AE that requires a dose reduction, a patient does not have recurrence of the same event that caused the dose reduction within 2 cycles of the start of the lower dose. Dose re-escalation is not permitted when dose reduction is for Grade 4 nonhematologic toxicities as required per dose modification guidelines below (Table 8.c).

8.2.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

TAK-659 is administered in continuous cycles; therefore, study drug should be administered continuously unless AEs occur that meet the dose modification criteria as outlined below (Table 8.b, Table 8.c).

8.2.4 TAK-659 Dose Modification for Hematologic Toxicities

Please refer to Table 8.b for dose delay and reduction recommendations for hematologic toxicities. When the dose of TAK-659 is withheld on the basis of the criteria in Table 8.b, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to Grade ≤1 or baseline values. Upon recovery, TAK-659 may be re-initiated either at the same dose level or at a reduced dose level. When there are transient laboratory value abnormalities that, per investigator assessment, are not clinically significant or are related to the disease and not

the drug, continuation of therapy without following the dose modification guidelines is permissible upon discussion with the sponsor.

Table 8.b TAK-659 Dose Adjustments for Hematologic Toxicities

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <1500 cells/mm^3)	Maintain dose level.
Grade 2 (ANC 1000-1499 cells/mm^3)	Maintain dose level.
Grade 3 (ANC 500-999 cells/mm^3)	Withhold dose until resolved to Grade ≤1 (ANC ≥1500 cells/mm^3) or baseline value, then: • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level. • If recurred, reduce dose by 1 dose level.
Grade 4 (ANC <500 cells/mm^3)	Withhold dose until resolved to Grade ≤1 (ANC ≥1500 cells/mm^3) or baseline value, then reduce dose by 1 dose level.
Febrile neutropenia (ANC <1000 cells/mm^3, fever ≥38.5°C)	Withhold dose until resolved to Grade ≤1 (ANC ≥1500 cells/mm^3) or baseline value and fever/infection recovered, then reduce by 1 dose level.
Thrombocytopenia (PLT)	
Grade 1 (PLT <75,000 cells/mm^3)	Maintain dose level.
Grade 2 (PLT 50,000-74,999 cells/mm^3)	Maintain dose level.
Grade 3 (PLT 25,000-49,999 cells/mm^3)	Withhold dose until resolved to Grade ≤1 (PLT ≥75,000 cells/mm^3) or baseline value, then: • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level.
Grade 4 (PLT <25,000 cells/mm^3)	Withhold dose until resolved to Grade ≤1 or baseline value, then reduce by 1 dose level.
Grade 3 anemia	Withhold dose until resolved to Grade ≤1 or baseline value, then: • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level.
Grade 4 anemia	Withhold dose until resolved to Grade ≤1 or baseline value, then reduce by 1 dose level if patient is not discontinued (see Section 8.2.1 and Section 9.7 for reasons for discontinuation).

PLT=platelets.

8.2.5 TAK-659 Dose Modification for Nonhematologic Toxicities

Please refer to Table 8.c for dose hold and dose reduction recommendations for nonhematologic toxicities. When the dose of TAK-659 is withheld on the basis of the criteria in Table 8.c, clinical

and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to Grade ≤1 or baseline values. Upon recovery, TAK-659 may be re-initiated either at the same dose level or at a reduced dose level. When there are transient laboratory value abnormalities that, per investigator assessment, are not clinically significant or are related to disease and not the drug, continuation of therapy without following the dose modification guidelines is permissible upon discussion with the sponsor.

Table 8.c TAK-659 Dose Adjustments for Nonhematologic Toxicities

Criteria	Action
All Grade 3 nonhematologic toxicities, including suspected pneumonitis, with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to Grade ≤1 or baseline values within 48 hours with optimal antiemetics and antidiarrheal following standard of care. • Transient Grade 3 fatigue (lasting <72 hours). • Asymptomatic lipase elevation (Grade <4) in the absence of significant amylase elevation (Grade <3). • Asymptomatic amylase elevation (Grade <4) in the absence of lipase elevation (Grade <3). • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3). • Grade 3 hypophosphatemia resolved to Grade ≤1 or baseline value within 72 hours with phosphate repletion. • Other Grade 3 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigator.	Hold TAK-659 until resolution to Grade ≤1 or baseline values, then: • If resolved in ≤7 days, maintain the dose level. • If resolved in >7 days, reduce dose by 1 dose level. • If recurs, reduce dose by 1 dose level. For the 7 exceptions, maintain the dose level (no dose hold required).
Grade 4 nonhematologic toxicities, including suspected pneumonitis, with the exception of: • Asymptomatic Grade 4 lipase elevation in the absence of significant amylase elevation (Grade <3). • Asymptomatic Grade 4 amylase elevation in the absence of significant lipase elevation (Grade <3). • Asymptomatic Grade 4 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (Grade <3). • Grade 4 hypophosphatemia resolved to Grade ≤1 or baseline value within 72 hours with phosphate repletion. • Other Grade 4 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigator.	Consider permanently discontinuing TAK-659 (see Section 8.2.1 and Section 9.7 for reasons for discontinuation), except when the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the medical monitor or designee. Dose reduction of ≥1 dose level is required if study treatment resumes after resolution to Grade ≤1 or baseline values. For the exceptions, hold TAK-659 until resolution to Grade ≤1 or baseline values, then: • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level. • If recurs, reduce dose by 1 dose level.

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Grade 4 nonhematologic toxicities, with the exception of asymptomatic laboratory changes, will in general require that treatment with TAK-659 be permanently discontinued. If, in the opinion of the investigator and the sponsor (project clinician or designee), it is in the patient's best interest to continue treatment with TAK-659, the dose of TAK-659 will be reduced by at least 1 dose level when treatment resumes after recovery from the toxicity or toxicities in question to Grade 1 or to baseline values. When a dose reduction of TAK-659 is required because of Grade 4 nonhematologic toxicities, no re-escalation of dose will be permitted. For Grade 4 asymptomatic laboratory abnormalities (eg, lipase, amylase, AST, ALT, or CPK), TAK-659 should be held until resolution to Grade ≤1 or baseline values. When study drug is resumed, TAK-659 can be started at the same or a reduced dose level, depending on how quickly the AE resolves. If a dose reduction is required, no dose re-escalation is permitted in this situation.

8.2.6 Criteria for Dose Escalation During Stage 1 Ramp-up

To provide patients the opportunity to derive maximum clinical benefit (without prohibitive toxicity), the starting dose of 60 mg QD could be increased to 80 mg QD at Cycle 2 Day 1, then increased to 100 mg QD at Cycle 3 Day 1, provided that there have been no drug-related AEs that require dose modification per protocol.

At the end of each cycle during the ramp-up, patients will be assessed for their suitability to dose-escalate to the next level based on safety and tolerability. If the patient experiences any drug-related AEs that require dose modification (inclusive of dose held and dose reduction) per protocol in a given dose cycle, dose escalation will not proceed to the next level. If the AE(s) resolves, the patient may then restart dose escalation in the next cycle either at the same dose or a reduced dose according to the protocol-defined dose reduction criteria. In case that dose reduction is not required, when the patient resumes the study drug at the same dose, dose escalation to the next dose level and further to the full dose of 100 mg QD TAK-659 may be pursued if no recurrence of the same AE(s) or any other AEs leading to dose modification is observed in the next cycle of treatment. However, if the same AE(s) or different AE(s) requiring dose modification occur in two consecutive cycles at the same dose level, further dose escalation is not allowed. If the patient resumes the study drug at a reduced dose per protocol, no dose re-escalation is recommended.

8.3 Concomitant Medications and Procedures

During the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is taking or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

The following restrictions apply during the study:

- Any antineoplastic therapy other than TAK-659 is prohibited during the study. If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD) is not permitted during study. Palliative radiotherapy for local pain/symptom control in a preexisting nontarget lesion, if required, may be considered after discussion with the sponsor's clinical representative. Details of the palliative radiotherapy should be documented in the source records and eCRF, including dates of treatment, anatomical site, dose administered and fractionation schedule, and associated AEs.
- Chronic treatment with systemic steroids at dosages equivalent to prednisone >10 mg/day or other immunosuppressive agents is not permitted (except to treat drug-related AEs). Topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) are allowed.
- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) is not recommended during the first cycle. Patients who experience severe and/or febrile neutropenia during the study can be managed with growth factor support if needed, including prophylactic use of growth factor, in accordance with American Society of Clinical Oncology (ASCO) guidelines.
- Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A should be avoided in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix I for a nonexhaustive list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA draft guidance for DDI studies.
  - Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole.
  - Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin.
  - Antimycobacterials: rifabutin, rifampin, rifapentine.
  - Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone.
  - Antidepressant: nefazodone.
  - Immunosuppressant: cyclosporine.
  - Calcium channel blockers: diltiazem, felodipine, mibefradil, verapamil.
  - Antiarrhythmics: amiodarone, dronedarone, quinidine.
  - Antiplatelet: ticagrelor.
  - Antilipid: avasimibe.
  - Other cardiovascular: captopril, carvedilol, ranolazine.
  - Vasopressin antagonist: conivaptan.

– Food/herbals/supplements: grapefruit-containing food and beverages, St. John's wort, quercetin.

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and in Appendix I may be used for AE management if there is no appropriate alternative treatment available per the investigator's judgment and the dosing is not concurrent with study drug. This situation requires discussion between the investigator and the medical monitor, and the discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

Note that medications used to treat HIV or hepatitis C infection are not listed above or in Appendix I because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list above or in Appendix I, its use must be discussed with the medical monitor or designee to assess the relative benefit and risk.

8.4 Precautions and Restrictions

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-659 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner.

Nonsterilized female patients of childbearing potential and male patients should use highly effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients of childbearing potential must:

- Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the signing of the ICF through 180 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy, or not being postmenopausal for at least 1 year before screening visit (≥12 months of amenorrhea in the absence of other biological or physiological causes).

Male patients, even if surgically sterilized (ie, status postvasectomy), who are sexually active with partners who are of childbearing potential, must:

- Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

Male patients should not donate sperm from the time of signing the ICF through 180 days after the last dose of study drug.

8.5 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms per standard clinical practice are allowed, unless specifically excluded. Supportive care agents, such as erythropoietin, G-CSF, blood products (RBC and platelet transfusions), and pain medications, are permitted as needed per American Society of Hematology (ASH)/ASCO guidelines or local institutional practice; however, these agents should not be used in this study in a manner that would help establish eligibility for the study.

8.5.1 Prophylaxis Against Infection

Patients with advanced hematological malignancies may be at an increased risk of infection. Prophylactic use of antibiotic, antiviral, or antifungal medication can be considered as clinically indicated and per local standard practice. In particular, lymphopenia can develop in association with either treatment or the underlying disease (DLBCL). Lymphopenia can be associated with reactivation of herpes zoster, CMV, herpes simplex, and other viruses. Antiviral therapy such as acyclovir, ganciclovir, valacyclovir, or other antiviral agents may be initiated as clinically indicated. Testing of CMV replication by a local polymerase chain reaction (PCR) assay will be required at Baseline, and further monitoring and prophylactic or preemptive therapy to asymptomatic patients, if indicated, should follow the institutional standard practice. The following agents should be considered for prophylaxis or preemptive treatment against CMV: ganciclovir intravenously (IV), valganciclovir (PO), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until CMV is no longer detected by PCR.

Patients with lymphopenia may also be more prone to developing infections, such as respiratory tract infections or pneumonia. Consider a diagnosis of opportunistic infection including PJP in patients presenting with shortness of breath, cough, or fever. Prophylaxis for PJP must be initiated (either at Baseline or during treatment) if the following are present:

- Absolute $CD4^+$ T-cell count of $<200/mm^3$.
- Percentage of $CD4^+$ T cells <20%.
- Prior episode of PJP in medical history.

For older patients; patients with recent exposure to steroids, rituximab, cyclophosphamide, or immunosuppressive agents; or patients who, in the investigator's opinion, are more susceptible to opportunistic infection at Baseline, PJP prophylaxis should be considered at the start of study treatment. When steroids or any immunomodulatory agents need to be used to manage AEs during the study, PJP prophylaxis should be considered when the study treatment resumes or is co-administered. Trimethoprim-sulfamethoxazole is recommended as the treatment of choice for PJP prophylaxis unless contraindicated; however, investigator discretion in selecting a more appropriate prophylaxis regimen for their patients is permitted.

Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the patient is prone to developing neutropenia; however, the use of such agents should be at the discretion of investigators and based on the local standard practice. Patients who develop neutropenic fever should be evaluated promptly and treated immediately with parenteral antibiotics tailored to the prominent organisms and resistance patterns of the institution.

8.5.2 Pneumonitis

Patients with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis after ruling out infectious causes and alternative etiologies. If pneumonitis is suspected, TAK-659 treatment should be interrupted and the patient treated per standard of care. If pneumonitis is moderate or severe, discontinue TAK-659. Patients should be monitored for respiratory signs and symptoms throughout treatment and be advised to promptly report respiratory symptoms.

8.5.3 Nausea and/or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation; however, a patient who develops nausea or vomiting will be actively managed by employing optimal antiemetic treatment per local standard practice. Additionally, antiemetics could be used prophylactically as clinically indicated following the first occurrence of TAK-659–related or possibly related nausea or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules.

8.5.4 Diarrhea

Prophylactic antidiarrheals will not be used in this study; however, patients should be instructed to take loperamide or comparable antidiarrheal medication according to institutional or local practice, once infectious causes are ruled out. Adequate fluid intake should be maintained to avoid dehydration, and any fluid deficit should be corrected before initiation of treatment with study drug and during treatment.

8.5.5 Edema (Including Periorbital)

Peripheral and periorbital edema have been observed in patients treated with TAK-659. Management of the event, if it occurs, should follow the standard local practice, and dose modification should proceed according to the dose modification guidelines in Table 8.c.

8.5.6 Rash With or Without Pruritus

Prophylactic measures should be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤10 mg per day or equivalent) is permitted. Treatment with TAK-659 must be withheld for Grade 3 or 4 rash. Refer to dose modification guidelines in Table 8.c.

8.5.7 Thrombocytopenia

Blood counts should be monitored regularly as outlined in Appendix A with additional testing obtained according to standard clinical practice. Administration of TAK-659 should be modified per dose modification guidance in the protocol when thrombocytopenia occurs (see Table 8.b). Platelet transfusion is allowed to manage severe thrombocytopenia and to prevent and minimize bleeding according to ASH/ASCO guidelines. In general, platelet transfusion should be given prophylactically to patients with platelet counts <10,000/μL or to any patients with signs of overt bleeding, such as oral purpura. Each transfusion episode, including the type of transfusion (platelets), should be recorded.

8.5.8 Neutropenia

Blood counts should be monitored regularly as outlined in Appendix A with additional testing obtained according to standard clinical practice. TAK-659 administration should be modified per dose modification recommendations in the protocol when neutropenia occurs (see Table 8.b). Myeloid growth factors (eg, G-CSF, GM-CSF) may be used to treat severe or febrile neutropenia according to ASCO guidelines; however, it should be noted that prophylactic use of myeloid growth factors should be avoided during the first cycle (see Section 8.2.6).

8.5.9 Anemia

Hemoglobin should be monitored regularly as outlined in Appendix A with additional testing obtained according to standard clinical practice. Packed RBC transfusion is permitted, as necessary, per local institutional practice. In general, RBC transfusion is recommended for all symptomatic patients with anemia, and any asymptomatic patients with hemoglobin ≤7 to 8 g/dL, with the purpose of maintaining the hemoglobin between 8 and 10 g/dL, depending on the patient's age, symptoms, and comorbid conditions. Each transfusion episode, including the type of transfusion (RBC), should be recorded. Erythropoietic agent use at the investigator's discretion is also allowed and should be administered according to institutional practice.

8.5.10 Hypophosphatemia

Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise, refer to dose modification guidelines in Table 8.c.

8.5.11 Enzyme Elevations

8.5.11.1 Transaminase, Amylase, Lipase, and CPK Elevations

Elevations of transaminases, amylase, lipase, and CPK have been observed. Events are generally asymptomatic and reversible with dose interruption. See dose modification guidelines in Table 8.c.

8.5.11.2 LDH Elevations

LDH elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic, and their clinical significance is unknown. No action, such as dose interruption, has been taken as a result of increased LDH; however, LDH elevation is reversible on the basis of experience in patients who had TAK-659 interrupted for other reasons.

8.6 Blinding and Unblinding

This is an open-label study.

8.7 Description of Investigational Agents

TAK-659 has been formulated into immediate-release, film-coated tablets via a common granulation process. Two different tablet dosage strengths, 20 mg and 100 mg, were formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets were coated with Opadry film coat.

8.8 Preparation, Reconstitution, and Dispensation

Detailed instructions for dispensing TAK-659 immediate-release film-coated tablets are provided in the Pharmacy Manual.

TAK-659 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-659.

8.9 Packaging and Labeling

TAK-659 20 mg and 100 mg tablets will be packaged into round, white, high-density polyethylene bottles with induction seals, desiccant packs, and polypropylene child resistant caps. Each bottle of TAK-659 will be labeled with either a single-panel or multilanguage label containing pertinent study information, country-specific requirements, and a caution statement.

8.10 Storage, Handling, and Accountability

TAK-659 tablets should be stored in the original dispensing bottles at 1°C to 25°C (33.8°F to 77°F) with excursions permitted to 30°C (86°F) as long as they do not exceed 7 days. All temperature excursions of the tablets must be reported back to the sponsor for assessment and determination for continued use. Refer to the Pharmacy Manual for additional information. The TAK-659 tablets must be used before the retest date indicated on the label or accompanying documentation. Throughout the clinical trial, the stability of the drug product will be monitored. TAK-659 tablets should remain in the original bottles provided to the investigational sites and patients. Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily.

Because TAK-659 is an investigational agent, it should be handled with due care. In the case of broken tablets, raising dust should be avoided during the clean-up operation. Damaged tablets may be harmful by inhalation, ingestion, or skin and/or eye contact. If damaged tablets come in contact with the eyes or skin, the area should be immediately and thoroughly flushed and washed for at least 15 minutes with water (and soap for skin). Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of TAK-659, including that TAK-659 is to be taken as intact tablets. Patients will receive diary cards to record dosing compliance. Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the Millennium Study Monitor or designee for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and the contract research organization (CRO) may be found in the Study Manual. A full list of investigators is available in the sponsor's or CRO's investigator database.

For 24-hour contact information, please refer to the Study Manual.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

This study is for efficacy evaluation purposes. Details around cohort assignment in Stage 1 will be described in the Study Manual.

9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, EOT, PFS follow-up, and OS follow-up. Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Procedures conducted during the Screening period that are performed within 3 days before Cycle 1 Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified.

Unless otherwise noted (see Section 8.1 and Table A), evaluations during the Treatment period must occur before study drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. Laboratory assessments and procedures may occur within ±3 days of the scheduled day for extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons); however, the timing of PK and pharmacodynamic assessments as specified in the Schedule of Events (Appendix A, Table A) is not flexible.

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The age, race, ethnicity, and sex of the patient are to be recorded during Screening.

9.4.3 Medical History

During the Screening period or on Cycle 1 Day 1 if the screening visit is >4 days prior, a complete medical history, including smoking history, will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.4.9.

9.4.4 Physical Examination

A physical examination, either complete or symptom directed, will be completed per standard of care at the times specified in the Schedule of Events (Appendix A).

9.4.5 Patient Height and Weight

Height will be measured only during Screening (within 28 days before the first dose of TAK-659).

Weight will be measured during the times specified in the Schedule of Events (Appendix A).

9.4.6 ECOG Performance Status

ECOG performance status is to be assessed at the times specified in the Schedule of Events (Appendix A).

9.4.7 Vital Signs

Vital sign measurements include seated (after 3 to 5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, oxygen saturation, and temperature.

9.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine pregnancy test will be performed predose on Day 1 of all cycles and at the EOT visit, and negative results must be obtained before the first dose of study drug may be administered. If the screening serum test is done within 3 days before the first dose of study drug in Cycle 1 and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request by an IEC/IRB, or if required by local regulations.

9.4.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient and their outcomes will be recorded in the eCRF from the time the ICF is signed through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.3 for a list of concomitant medications and procedures to be avoided during the study unless otherwise specified.

9.4.10 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

9.4.11 Enrollment

A patient is considered to be enrolled in the study when the first dose of TAK-659 has been administered.

Procedures for completing the enrollment information are described in the Study Manual.

9.4.12 Electrocardiogram

A 12-lead ECG will be administered at the time points specified in the Schedule of Events (Appendix A).

Unless otherwise specified, all scheduled ECGs should be performed predose and after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

Confirmation that the machine estimates of the rate-corrected QT interval (milliseconds) of electrocardiograph (QTc) are accurate using the appropriate QT correction formula (Fridericia's correction [QTcF], Bazett's corrected QT interval [QTcB]) should be performed. Estimates of QTc for study eligibility should use QTcF. If a QTc value confirmed by the qualified reader is >475 msec, an evaluation to determine etiology should be conducted. If the prolonged QTc finding can be corrected with a change in medication and/or correction of electrolyte abnormalities, and a repeat ECG meets eligibility requirements, the patient may enroll to the study upon review and agreement by the sponsor's clinician.

Following initiation of treatment, if a QTc value is confirmed by a qualified reader as >500 msec for any ECG, the following will occur:

- The sponsor's clinician or designee will be promptly notified.
- TAK-659 should be held, and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).

- A formal consult by a cardiologist should be considered. Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.

The decision of whether to reinitiate TAK-659 treatment with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc >500 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated TAK-659, and appear to have benefited from TAK-659 treatment with either disease control or response will be agreed to by the investigator and the sponsor's clinician on a case-by-case basis.

The ECGs performed should be reviewed by the investigator or delegate before the patient leaves the clinic on visit days.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally. Handling and shipment of clinical laboratory samples are outlined in the Study Manual and Laboratory Manual. Additionally, the following safety laboratory tests should be performed locally for dosing decisions: standard hematology (with white blood cell differential count), AST, ALT, total bilirubin, creatinine, creatinine kinase, amylase, and lipase. Additional local laboratory tests should be considered on the basis of the AEs that are being monitored and may influence the dose decision.

Clinical laboratory evaluations will be performed as outlined below:

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the Schedule of Events (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	γ-Glutamyl transferase (GGT)
Hemoglobin	Alkaline phosphatase (ALP)	Glucose
Leukocytes with differential	ALT	Glycosylated hemoglobin (HbA1c)
Neutrophils (ANC)	Amylase	Lactate dehydrogenase (LDH)
Platelet (count)	AST	(including LDH isozymes)
Lymphocytes (absolute lymphocyte count [ALC])	Bilirubin (total)	Lipase
	Blood urea nitrogen (BUN)	Magnesium
Lymphocyte subsets (CD4, CD8, CD4:CD8 ratio)	Calcium	Phosphate
	Carbon dioxide (CO_2)	Potassium
	Creatinine	Sodium
	Creatine kinase (CK)	Total protein
	Chloride	Urate

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

When creatinine clearance is estimated, the Cockroft-Gault formula will be employed as follows (Appendix F):

$$Estimated\ creatinine\ clearance = [(140 - Age) * Mass(kg)\ ]/[72 * serum\ creatinine\ (mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.14 Ophthalmic Exam

A slit lamp eye examination will be performed by an ophthalmologist at Screening; on Cycle 2 Day 1, Cycle 7 Day 1, and every 6 cycles thereafter (±2 weeks); and at EOT. On the basis of nonclinical toxicology findings with TAK-659 in rats, slit lamp examinations should focus on detecting any posttreatment changes in ocular lenses. Examination and photographing of the retina will be performed at Baseline but not during the study unless clinically indicated. Additional eye exams may also be performed as required. Additionally, patients will be carefully monitored for eye complaints at each visit and instructed to report visual symptoms as soon as they occur.

9.4.15 Disease Assessment

Efficacy will be assessed by an IRC. The membership of the IRC and the rules for review will be constituted by a protocol-specific charter; response will be assessed using both modified 2007 IWG criteria for malignant lymphoma (Appendix D) [16] and the 2014 IWG (Lugano) criteria [15] at Screening; on Days 22 to 29 (predose) of Cycles 1, 3, and 6; every 3 cycles through Cycle 24; and every 6 cycles thereafter (until PD or start of alternative therapies). Patients who discontinue treatment and do not have previously documented radiographic PD will undergo an imaging assessment at the EOT visit. The ORR assessment based on the modified 2007 IWG criteria [16] will support the primary endpoint analysis for the study, and ORR based on the 2014 IWG (Lugano) criteria [15] will support the secondary endpoint. Response will also continue to be assessed in PFS follow-up every 3 months for patients who discontinue treatment for reasons other than PD until occurrence of PD, start of alternative therapy, or conclusion of the study, whichever occurs first.

Response assessments should include radiographic imaging (CT/MRI and FDG-PET), evaluation of symptoms, and bone marrow aspirate/biopsy if appropriate (see details below) [15]. The FDG-PET imaging should be done minimally at Screening and at the end of Cycles 1, 3, and 6, or if clinically indicated (see Schedule of Events [Appendix A]). Central collection of images at

imaging time points by sponsor or designee is required. Investigator assessment of response following the modified 2007 IWG criteria will also be collected per the Schedule of Events (Appendix A).

Two modifications to the 2007 IWG criteria will be instituted in this study:

- When assessing response, special consideration should be given to a situation where a patient may have had study drug held between the 2 scheduled imaging scans for ≥2 weeks because of AEs or other circumstances. If at the time of response assessment, metabolic changes are observed on a patient's positron emission tomography (PET) scan (ie, increased or new FDG uptake) that are not consistent with lesion changes indicative of PD by CT scan, discontinuation of study treatment is not recommended. It is recommended that the patient instead receive an additional cycle of treatment and that another response assessment be performed at the end of that cycle. If the metabolic changes observed on PET scans (ie, increased or new FDG uptake) remain, this result would be consistent with PD, and the patient should be discontinued from the study. If the previous metabolic changes observed on PET scan resolve and there is no indication of PD by CT or other measures, then the patient may remain on study.
- If PET-CT indicates bone marrow involvement at Baseline, bone marrow biopsy is not required. Negative FDG-PET avidity is adequate to confirm CR in these patients. If FDG-PET does not suggest baseline bone marrow involvement, a bone marrow biopsy is then required, and repeat biopsy to confirm CR is also needed.

If a patient has been on study for 2 years (on treatment), response will be assessed every 6 months. Patients in PFS follow-up will be assessed for response every 3 months irrespective of duration on study. When patients discontinue for reasons other than PD, PFS follow-up requires disease assessment every 3 months, regardless of what the frequency of assessments was at the time of discontinuation.

9.4.15.1 CT Scans

CT scans of the chest, abdomen, and pelvis (neck should be included, if appropriate) will be performed to assess disease at Screening and per the assessment schedule noted above and in the Schedule of Events (Appendix A). All CT scans should be performed with IV contrast, and abdominal and pelvic CT scans should also be performed with oral contrast, unless contrast is contraindicated. Hybrid PET-CT scanners may be used to acquire the required CT images only if CT produced by the scanner is of diagnostic quality, adheres to specified scan parameters, and includes IV contrast (unless medically contraindicated). Nondiagnostic CT images acquired for attenuation purposes during PET-CT are NOT acceptable as the only CT scan for the time point. Diagnostic CT images with contrast (unless medically contraindicated) with a standalone CT scanner must be acquired if PET-CT is unable to acquire diagnostic CT images. If the diagnostic CT and PET are acquired on the same day, it is strongly recommended that the PET be performed before the CT with IV contrast to avoid compromising PET results [15]. MRI may be performed in place of CT if CT is contraindicated; however the same modality that is used at baseline should be used for subsequent timepoints to maintain consistency.

9.4.15.2 PET Scans

A PET scan with FDG extending from the neck through the mid thighs will be performed to assess disease as noted in the Schedule of Events (Appendix A). Examinations should be consistent across all time points, including amount of tracer, location of injection, arm position, and scan delay. After Cycle 12, PET scans will be performed only if needed to follow the disease, confirm the CR or PD status, or as indicated clinically. Note that if a patient achieves CR, PET scans are not required at subsequent assessments. The Deauville 5-point scale will be used to assess PET avidity [15].

9.4.15.3 Bone Marrow Biopsy and Aspirate

A bone marrow biopsy will be performed at Screening to assess disease only in patients with baseline PET-CT indicating negative bone marrow involvement, and will be repeated to confirm CR if the screening evaluation was positive and other criteria for CR have been met, or at the time of suspected PD per standard practice. If bone marrow involvement is indeterminate by morphology, IHC evaluation of the biopsy material should be negative for assessment as CR. If bone marrow involvement is identified using PET-CT at Baseline, PET-CT evaluation to rule out FDG-avid disease in bone marrow is sufficient to confirm CR. A biopsy could be performed at EOT (optional to patients) if the initial biopsy was positive and a response has been achieved but relapse subsequently documented.

9.4.16 Tumor Biopsies

9.4.16.1 Banked Tumor Specimen Measurements

Archival (banked) tumor tissue samples should be obtained at Screening, if available, for all patients enrolled to identify candidate biomarkers predictive of clinical response to TAK-659. A tumor pathology block or at least 20 unstained slides is required. Archival FFPE tumor tissue obtained at the time of the patient's original diagnosis or during the course of disease (eg, at the time of relapse from last prior therapy), and FFPE tissue from the fresh tumor biopsy performed as part of the screening procedure to confirm the DLBCL diagnosis for eligibility, are acceptable specimens.

The banked sample collection is to support retrospective analysis of various genomic/genetic biomarkers or pathway signatures to identify potential predictive biomarkers significantly associated with clinical response to TAK-659 in patients with DLBCL. Biomarkers to be investigated include, but are not limited to, BCR/SYK pathway molecules; BCR gene expression profiles; tumor-specific somatic gene alterations; other disease-relevant biomarkers such as BCL-2, MYC, BCL-6, and Ki-67; and known subtype classifications, such as ABC and GCB types for patients with DLBCL.

9.4.16.2 Fresh Tumor Biopsies

All patients will undergo fresh tumor biopsy during Screening unless the patient does not have a safely accessible lesion and a fresh biopsy procedure would put the patient at unjustifiable risk.

Optional tumor biopsies may be obtained from consenting patients at any time during the study as determined by the investigator when patients have responded or responded and relapsed. The biopsy material will be submitted for local pathology review to confirm diagnosis of DLBCL to support the eligibility evaluation for the patient. CCI [redacted]. If a patient has had a biopsy that confirms the DLBCL diagnosis for eligibility performed within 1 month (≤30 days) before Cycle 1 Day 1 or between the completion of previous treatment and the Screening period of this study, no additional biopsy will be required pending the availability of a sufficient amount of archival tumor tissue for local pathology confirmation and biomarker studies. If the available archival tumor tissue sample is not sufficient, additional discussion will need to take place with the sponsor or designee, and a fresh tumor biopsy may be requested. If a patient has neither a safely accessible lesion for fresh biopsy nor archival biopsy samples obtained between the completion of previous treatment and the Screening period, upon approval from the sponsor or designee, the confirmation of a DLBCL diagnosis for the patient may be based on an archival specimen supporting a prior DLBCL diagnosis for the purpose of fulfilling eligibility.

Optional fresh tumor biopsies can be requested during the study (eg, when patients have responded or responded and relapsed) for the purpose of exploratory biomarker studies if the patient agrees to the procedure and signs an informed consent.

CCI [redacted]

Patients who undergo biopsy of tumor tissue must have adequate platelet function per investigator assessment, an activated partial thromboplastin time and a prothrombin time within the normal range, and no history of excessive bleeding or recent exposure to antiplatelet or anticoagulant therapy (eg, clopidogrel [Plavix] or salicylates [aspirin] in the prior 7 days). The tumor biopsy procedure will be performed under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible.

9.4.17 Analysis of ctDNA

Plasma samples will be collected from all patients as indicated in the Schedule of Events (Appendix A), and plasma will be extracted to obtain ctDNA. Changes in the amount of purified

ctDNA may be quantified and monitored during the course of treatment. In addition, ctDNA may be subjected to analysis of genetic alterations (mutations, translocations, amplifications) using an appropriate platform, such as next-generation sequencing.

9.4.18 Analysis of Cytokines/Chemokines

Serum samples will be collected from all patients for pharmacodynamic evaluation as indicated in the Schedule of Events (Appendix A, Table A), and the cytokines/chemokines in serum will be measured. Posttreatment changes in the amount of cytokines/chemokines will be assessed, and their correlation with clinical response will be analyzed.

9.4.19 Analysis of Immune Cells in Peripheral Blood

CCI [redacted]

9.4.20 PK Measurements

Blood samples for the determination of TAK-659 plasma concentrations will be obtained during Cycles 1 through 4 at the following time points via a limited (sparse) sampling strategy (refer to Appendix A, Table A, for additional details):

- Cycle 1 Day 1: predose (within 1 hour before dosing).
- Cycle 1 Day 1: 2 to 4 hours postdose.
- Cycle 1 Day 8: any time during the scheduled clinic visit after TAK-659 administration at home.
- Cycle 1 Day 15: predose (immediately before dosing).
- Cycle 1 Day 15: 2 to 4 hours postdose.
- Cycle 1 Day 22: predose (immediately before dosing).
- Cycle 1 Day 22: 2 to 4 hours postdose.
- Cycle 2 Day 1: predose (immediately before dosing).
- Cycle 2 Day 1: 2 to 4 hours postdose (for dose titration patients only).
- Cycle 2 Day 15 predose (immediately before dosing, for dose titration patients only).
- Cycle 2 Day 15: 2 to 4 hours postdose (for dose titration patients only).
- Cycle 3 Day 1: predose (immediately before dosing).
- Cycle 3 Day 1: 2 to 4 hours postdose (for dose titration patients only).
- Cycle 3 Day 15: predose (immediately before dosing, for dosing titration patients only).
- Cycle 3 Day 15: 2 to 4 hours postdose (for dose titration patients only).

- Cycle 4 Day 1: predose (immediately before dosing).

For clinic visits where predose PK samples are to be collected, patients will be instructed to refrain from taking their TAK-659 dose at home before the clinic visit. At these visits, predose PK samples will be collected before TAK-659 dosing. For the Cycle 1 Day 8 visit, patients should be instructed to take their TAK-659 dose at home before the clinic visit. At this visit, the PK sample can be collected at any time during the clinic visit. A distribution of visit times during the day across patients is to be encouraged to ensure a range of postdose PK sampling times across the study population.

Details about collecting, processing, storing, and shipping the PK samples are provided in the Laboratory Manual.

The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on PK sample collection days. In addition, the dates and exact times of TAK-659 dosing (from patient diaries) will be recorded in the eCRF for the 2 doses of TAK-659 administered before each PK sample collection day. Patients should be reminded to record dosing times in their diaries as instructed.

The primary aim of PK sampling in this study is to measure the plasma concentration of TAK-659; however, plasma samples collected for TAK-659 PK measurements may additionally be used for exploratory measurement of metabolites of TAK-659, if technically feasible and considered necessary for further understanding the metabolism and clearance of TAK-659.

9.4.21 DNA Measurements

At Screening, 3 buccal epithelial cell samples will be obtained from patients. CCI [redacted]

9.4.22 CMV Testing

A blood sample will be obtained during Screening for the determination of CMV replication per local PCR; however, a sample will also be collected for central testing at this time point. The local CMV viral load data will be entered into the eCRF along with the normal range for the local assay. Further monitoring and prophylaxis or preemptive treatment against CMV in asymptomatic patients, if indicated, will follow the local standard practice.

9.5 Completion of Study Treatment (for Individual Patients)

For the purpose of the primary analysis, patients will be considered to have completed study treatment if they have an opportunity to complete 6 cycles of treatment with TAK-659 or if they experience PD.

9.6 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if:

- They are followed until death or the conclusion of the study, whichever occurs first.
- They remain on study treatment free of PD until the start of alternative therapy or the conclusion of the study, whichever occurs first.
- They continue on to the survival follow-up after discontinuation of the study drug.
- They discontinue study treatment while in CR and continue on to the follow-up for PD, and either:
  - Experience PD, or
  - Reach the end of the follow-up period.
- The sponsor terminates the study.

9.7 Discontinuation of Treatment With Study Drug

Treatment with study drug must be discontinued for any of the following reasons:

- Occurrence of drug-related Grade 4 nonhematologic toxicity or Grade 4 anemia, or other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.2.
- If dosing of TAK-659 is interrupted for >21 days for study drug-related or possibly related AEs despite supportive treatment per standard clinical practice. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit and risk assessment).
- If more than 2 dose reductions are required for a patient.
- Occurrence of AEs, resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the patient (if applicable).
- Disease progression per 2007 and/or 2014 IWG criteria as determined by the investigator (see Section 9.4.15).
- Use of a nonpermitted concomitant drug, as defined in Section 8.3, in which the predefined consequence is withdrawal from treatment. (The sponsor should be contacted to discuss whether trial treatment must be discontinued.)
- Occurrence of pregnancy (if applicable).

- Symptomatic deterioration (at investigator's discretion).
- Initiation of hematopoietic stem cell transplant.
- Withdrawal of consent by patient.
- Patient is lost to follow-up.

Because of medical need, it is permissible per protocol for a patient to start the study treatment before pathological confirmation of the DLBCL diagnosis as long as the diagnosis is confirmed within 4 weeks after Cycle 1 Day 1 dosing. If the diagnosis of DLBCL is not confirmed, or the histological subtype of DLBCL is not confirmed to be an eligible type for the study, the patient will be replaced. If a patient, after being enrolled and dosed with the study drug, is found to have failed to meet all eligibility criteria at Baseline, the patient will be replaced. Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF. Patients who do not have a confirmed diagnosis of DLBCL will continue to receive treatment until PD, unacceptable toxicity, or withdrawal from the study.

9.8 Withdrawal of Patients From Study

Patients may discontinue the trial at any time without giving a reason(s).

A patient must be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by patient.
- Participation in any other therapeutic trial during the treatment duration of this trial.
- Patient noncompliance with protocol.

9.9 Early Discontinuation of the Study

The sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Poor enrollment of patients, making completion of the trial within an acceptable timeframe unlikely.
- Plans to modify or discontinue the development of the study drug.

The sponsor will notify the investigator if the sponsor decides to discontinue the study.

9.10 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Patients will be given a diary to record study drug dosing.

The dosing diary will provide supporting information, if necessary. The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the patient may continue the study at the discretion of the investigator and after consultation with the Millennium clinician or designee. The timing of PK and pharmacodynamic assessments, however, as specified in the Schedule of Events (Appendix A, Table A) is not flexible.

If a dose of TAK-659 is held for up to 21 days for reasons unrelated to toxicity, the patient may be discontinued from the study following a discussion between the investigator and the sponsor.

9.11 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 3 months after the last dose of study drug or until PD, the start of alternative therapy, or the conclusion of the study, whichever occurs first. After the occurrence of PD, patients will continue to have OS follow-up visits. The OS information will be collected every 3 months after the last dose of study drug until death or the conclusion of the study, whichever occurs first.

Survivor information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieval from online or other databases (eg, social security indexes). In addition, data about the start of other anticancer therapies will be collected.

If a patient has transitioned to either ASCT or allogeneic stem cell transplant during this follow-up period, transplant details will also be collected in the eCRF including, but not limited to, type of transplant and success of transplant.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

A PTE is any untoward medical occurrence in a patient who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from Baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, the AE may jeopardize the patient, require medical or surgical intervention to prevent the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein disease or transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, effective date 27 November 2017 [17]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Cognizant

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

All Other Countries (Rest of World)

Fax #: 1-202-315-3560

E-mail: takedaoncocases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, effective date 27 November 2017 [17]. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of the ICF through 28 days after administration of the last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first, and recorded in the eCRFs.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF up to the first dose of study drug and will be recorded in the eCRFs.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF through 28 days after administration of the last dose of study drug and recorded in the eCRFs. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email address provided below.

Call Center	Phone Number	Email	Fax
DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 10.2)

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 calendar days for fatal and life-threatening events and 15 calendar days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues

where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site will also forward a copy of all expedited reports to its IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 IRC

An independent radiologic review committee (IRC) will review all disease evaluation data between Screening and PD (including the PFS follow-up period) from the study and determine disease status (response and progression). Data from the IRC will not be provided back to the investigator during the conduct of the study.

11.2 Steering Committee

The SSC will comprise a subset of investigators and sponsor personnel involved in the study or other external lymphoma key opinion leaders. The SSC will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality. The SSC will make recommendations of the Stage 2 dose regimen selection upon completion of Stage 1 and any necessary modifications to the protocol. The SSC charter will define the responsibilities of the committee.

11.3 Independent Data Monitoring Committee

The study will not have an independent data monitoring committee.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years

after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before the dose exploration analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Populations

DLBCL Population

The DLBCL population includes all patients who have a confirmed DLBCL diagnosis and who receive at least 1 dose of TAK-659. The DLBCL population will be used for primary and secondary efficacy analysis, and for additional efficacy analyses.

Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all patients who receive at least 1 dose of TAK-659. The mITT will be used for the sensitivity analyses for the efficacy analyses.

Per-Protocol Population

The per-protocol population includes all patients who receive at least 1 dose of TAK-659 and who have measurable disease at Baseline and no other major protocol deviations that could potentially affect tumor response.

Safety Population

The safety population includes all patients who receive at least 1 dose of TAK-659. The safety population will be used for all baseline characteristics, safety analyses, and exposure analysis.

Response-Evaluable Population

The response-evaluable population includes all patients who receive at least 1 dose of TAK-659 and have measurable disease at Baseline and least 1 postbaseline disease assessment. The response-evaluable analysis set will be used for sensitivity analyses of efficacy endpoints that are related to response, such as ORR, CR, and DOR.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics, including age, gender, race, weight, height, and other parameters, will be summarized using descriptive statistics.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Analysis

The primary endpoint for this study is ORR as assessed by IRC according to modified 2007 IWG criteria for malignant lymphoma [16] (Stage 2). Overall response is defined as a CR or PR. ORR is the proportion of patients who have overall responses. This primary efficacy hypothesis will be

tested using the null hypothesis that ORR for TAK-659 is <20% versus the alternative hypothesis that the ORR for TAK-659 is ≥20%. A 1-sided exact binomial test with a significance level of 0.025 will be used to test this hypothesis. Its associated 1-sided 97.5% CI will be calculated. For ease of interpretation, the 2-sided 95% CI of the ORR will also be calculated. Note that the 1-sided 97.5% CI and the lower bound of the 2-sided 95% CI will be the same. Also note that the primary efficacy analysis will be based on the DLBCL population using data from Stage 2.

Sensitivity analyses may be done for ORR using the mITT population, the 2014 IWG criteria [15], investigator-assessed responses, and the response-evaluable and per-protocol populations.

Subgroup analyses of ORR will be carried out using subgroups that will be defined in the SAP.

13.1.3.2 Key Secondary Efficacy Analysis

The key secondary efficacy endpoint is CR rate by IRC. The key secondary efficacy endpoint will be tested only if the primary efficacy endpoint of ORR per IRC is statistically significant. The key secondary efficacy hypothesis will be tested using the null hypothesis of CR rate less than 15% versus the alternative hypothesis of CR rate greater than or equal to 15%. If the primary endpoint is statistically significant, the key secondary endpoint will be tested at a 1- sided alpha of 0.025. Please note that the primary analysis for the key secondary endpoint is using the DLBCL population. Sensitivity analysis that is consistent with the sensitivity analysis for the primary endpoint may be done for the key secondary endpoints.

13.1.3.3 Secondary Efficacy Analysis

The secondary efficacy endpoints are:

- ORR per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).
- CR rate per IRC according to the 2014 IWG (Lugano) criteria [15] (Stage 2).
- ORR per IRC to select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1).
- ORR per IRC at 3, 6, and 9 cycles, respectively (Stage 2).
- DOR and duration of CR per IRC (Stage 2).
- ORR per IRC in patients with GCB DLBCL (Stage 2).
- ORR per IRC in patients with DLBCL transformed from indolent NHL (Stage 2).
- PFS per IRC (Stage 2).
- OS (Stage 2).

For response rate-related endpoints (such as ORR), main analyses for the rates will be performed using the DLBCL population (patient population is essentially the mITT population excluding patients without a confirmed DLBCL diagnosis) and data as measured by IRC per modified 2007 IWG criteria [16], with sensitivity analysis using the responses measured by IRC and 2014 IWG

(Lugano) criteria [15], and by the investigator, using the mITT population and the response-evaluable population.

Calculation of ORR at Cycle 3 (also 6 and 9) will include patients who are responders at Cycle 3 (also 6 and 9) as the numerator and the number of patients in the population as the denominator.

For duration of CR and duration of response, a Kaplan-Meier approach will be used.

PFS and OS will be estimated using the Kaplan-Meier approach using the DLBCL population. Sensitivity analysis for PFS using investigator responses and the mITT population, respectively, may be carried out.

Subgroup analyses of secondary endpoints will be carried out using subgroups that will be defined in the SAP.

13.1.4 PK Analysis

Plasma concentrations of TAK-659 will be listed by patient, dosing cycle and day, and nominal and actual time point. Descriptive statistics will be calculated for C_{trough} (observed concentration at the end of the dosing interval) in Cycle 1 to Cycle 4.

The plasma PK data collected in this study are intended to contribute to population PK and exposure–response analyses of TAK-659. These analyses may include data collected from other TAK-659 clinical studies. If applicable, the specifics of the population PK and exposure–response analyses will be described in separate SAPs, and results will be reported separately from the CSR for Study C34004.

13.1.5 Biomarker Analyses

CCI

[redacted]

13.1.6 Pharmacogenomic Analyses

CCI

[redacted]

13.1.7 Safety Analysis

AEs will be summarized using the safety population. No statistical testing or inferential statistics will be generated.

All AEs will be coded using the effective version of the MedDRA. Data will be summarized using Preferred Term and primary System Organ Class.

Exposure to study drug and reasons for discontinuation will be tabulated using the safety population. Safety will be evaluated using frequency of AEs, severity and type of AEs, and by changes from Baseline in the patient's vital signs, weight, ECGs, and clinical laboratory or instrumental examination results, using the safety population.

Treatment-emergent AEs (TEAEs) are defined as AEs that occur after administration of the first dose of study drug until 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

Summaries of AEs will include:

- TEAEs inclusive of all grades.
- Drug-related TEAEs inclusive of all grades.
- Grade 3 or higher TEAEs.
- Grade 3 or higher, drug-related TEAEs.
- SAEs.
- Drug-related SAEs.
- TEAEs leading to study drug discontinuation.

Descriptive statistics for actual values of clinical laboratory parameters, vital signs, and weight (and/or change from baseline values) over time will be calculated. Main laboratory values over time will be presented in graphs for key laboratory parameters.

Shift tables for laboratory parameters will be generated to show changes in NCI CTCAE grades from Baseline to worse postbaseline value. Graphical displays of key safety parameters may be used.

All concomitant medications collected from Screening throughout the study period will be classified to preferred terms according to the WHO drug dictionary.

A summary of ECG abnormalities will be presented by visit. ECG parameters (QT, QTcB, and QTcF; PR interval; QRS; and heart rate) will be summarized at each scheduled visit along with the mean change from Baseline to each posttreatment visit.

13.1.8 Dose Exploration Analysis

Dose exploration analysis will occur at the end of Stage 1. Assuming a historical control rate of 20% for ORR, 20 patients per dosing regimen are required to determine the dosing regimen for the phase 2 efficacy evaluation (Stage 2) portion of the study. Response data from both dosing regimens will be analyzed with a Bayesian model assuming prior of Beta(0.1,0.1) for each ORR. Dosing regimen A will be claimed ineffective if the posterior probability of ORR_A <20% is greater than the threshold of 0.75, likewise for dosing regimen B. If both regimens are deemed to be ineffective, termination of the study without proceeding to stage 2 may be considered. Other considerations for making this decision should be taken into account, including but not limited to sample size limitation, relevant data from other TAK-659 trials, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting. If only one dosing regimen is determined to be ineffective, then the other dosing regimen is chosen as the dosing regimen for the remaining portion of the study. If neither dosing regimen is claimed to be ineffective, then regimen A will be chosen if the posterior probability of ORR_A>ORR_B is greater than the threshold of 0.55, likewise dosing regimen B will be chosen if the posterior probability of ORR_B>ORR_A is greater than 0.55. If both the posterior probability of ORR_A>ORR_B and the posterior probability of ORR_B>ORR_A are ≤0.55, clinical and safety factors will be considered to choose the dosing regimen for Stage 2.

Consideration of an alternative dose regimen other than the two TAK-659 dose regimens evaluated in Stage 1 is permissible if supported by the Stage 1 data. For example, if the ramp-up dose schema (dose regimen B) is chosen based on the Bayesian model (see above) but majority of patients treated with dose regimen B fail to dose escalate beyond 60 mg QD TAK-659 following the dose escalation criteria, 60 mg QD TAK-659 may be considered as the dose for Stage 2. The Stage 1 data as well as other relevant supportive data from other trials of TAK-659 will be reviewed and discussed by the SSC. The stage 2 dose regimen of TAK-659 will be selected based on the recommendation by SSC upon agreement with the sponsor.

13.2 Interim Analysis and Criteria for Early Termination

The interim analysis will occur when approximately 40 patients with confirmed DLBCL are enrolled in Stage 2 whose response status can be adequately determined; ie, all 40 patients have either at least 1 posttreatment response evaluated or have been taken off study. At the interim analysis, if the posterior probability of ORR<20% is greater than the threshold of 0.75, the study will stop for futility; otherwise, the study will continue as planned until the final analysis.

The interim analysis will include only those patients with confirmed DLBCL who have taken at least 1 dose of TAK-659, have had the opportunity to receive at least 3 cycles of treatment, and

have at least 1 posttreatment response assessment. Patients who do not have a confirmed DLBCL diagnosis or patients who have been enrolled but did not have enough follow-up will not be included in the interim analysis.

13.3 Determination of Sample Size

For the lead-in dose exploration portion (Stage 1) of the study, assuming a historical control rate of 20% for ORR, at least 20 patients per dosing regimen are required to determine if either dosing regimen A or dosing regimen B is more effective.

For Stage 2 efficacy evaluation phase of the study, assuming a historical control rate of 20% for ORR and a TAK-659 ORR of 37%, this study will need to enroll at least 82 patients in Stage 2 to achieve 91% power at a 1-sided alpha level of 0.025, using an exact binomial test. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of treatment and have at least 1 posttreatment response evaluated, the interim analysis will be performed. The interim analysis will assess futility, and the study may either stop for futility (if posterior probability of ORR<20% is greater than the threshold of 0.75) or continue as planned.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the study-related procedures per protocol.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The patient must be given ample opportunity to (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the patient determines he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient at the time of consent and before the patient enters into the study. The patients should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the ICF in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to

the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the US FDA, the Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, patient name, address, and other identifier fields not collected on the patient's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas' investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Schedule of Events for Treatment

	Screening (a)	Cycle 1				Cycle 2		Cycle 3		Cycles ≥4	EOT	PFS/OS (b)
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	Day 1		
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical and smoking history	X	X (c)										
Complete physical examination	X											
Physical examination (either complete or symptom-directed)		X (c)	X	X	X	X	X	X	X	X	X	X (d)
Height	X											
Weight	X	X				X		X		X	X	
Vital signs (e)	X	X	X	X	X	X	X	X	X	X	X	X (d)
ECOG performance status	X	X				X		X		X	X	
12-Lead ECG (f)	X	X				X		X		X	X	
Response assessment for lymphoma by IWG (CT/FDG-PET) (g)	X				X (g)				X (g)	X (g)	X (g)	X (d)
Monitoring of concomitant medications and procedures	Recorded from signing of the ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.											
AE reporting	Recorded from signing of the ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.											
	SAEs (h) will be reported from signing of the ICF through 28 days after the last dose of study drug.											
TAK-659 administration (i)	TAK-659 is dosed PO QD every day.											
Patient diary review (j)		X	X	X	X	X	X	X	X	X	X	

Footnotes are on last table page.

Schedule of Events for Treatment

	Screening (a)	Cycle 1				Cycle 2		Cycle 3		Cycles ≥4	EOT	PFS/OS (b)
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15	Day 1		
Ophthalmic exam (k)	X					X				X (k)	X	
Pregnancy test (l)	X	X				X		X		X	X	
Hematology/chemistry (m)	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis (for hematuria and proteinuria evaluation) (m) (n)	X	X				X		X		X	X	
LDH isozymes (m)		X	X	X		X	X	X	X	X (o)		
CK testing (m)	X	X	X	X		X	X	X	X	X		
HbA1c (for patients who are hyperglycemic only (m)	X											
HIV, Hep B, Hep C tests (p)	X											
Plasma sample for ctDNA (q)	X									X	X	
Fresh tumor biopsy (r)	X											
Archival (banked) tumor tissue sample (r)	X											
Optional fresh tumor biopsy sample		X (s)										
CCI [redacted]												
Blood samples for PK (u)		X	X	X	X	X	X	X	X	X (v)		
CCI [redacted]												
CCI [redacted]												
CCI [redacted]												
CMV testing (z)	X											

Footnotes are on the following page.

AE=adverse event; CK=creatine kinase; CMV=cytomegalovirus; CT=computed tomography; ctDNA=circulating tumor DNA; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FDG-PET=[^{18}F]fluorodeoxyglucose-positron emission tomography; HbA1c=glycosylated hemoglobin; Hep B=hepatitis B virus; Hep C=hepatitis C virus; HIV=human immunodeficiency virus; IWG=International Working Group; LDH=lactate dehydrogenase; PK=pharmacokinetics.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor or designee for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor or designee.**

(a) Unless otherwise noted, the Screening visit must occur within 28 days before the day of the first dose of study drug (Cycle 1 Day 1). The ICF may be signed more than 28 days before Cycle 1 Day 1.

(b) Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 3 months from last dose of study drug until PD. Response will also continue to be assessed in PFS follow-up every 3 months for patients who discontinue treatment for reasons other than PD until occurrence of PD, start of alternative therapy, or conclusion of the study, whichever occurs first. After the occurrence of PD, patients will continue to have OS follow-up visits. The OS information will be collected every 3 months after the last dose of study drug until death or the conclusion of the study, whichever occurs first. For details about disease assessment, see footnote (g).

(c) The Cycle 1 Day1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (Cycle 1 Day 1).

(d) Required for PFS only.

(e) Perform vital signs (blood pressure, heart rate, temperature, and oxygen saturation) measurement before dosing. Vital signs include seated measurements.

(f) Single 12-lead ECGs will be performed at Screening, predose on Day 1 of each cycle, 2 hours postdose on Cycle 1 Day 1, Cycle 2 Day 1, >Cycle 4, and at EOT. ECGs should be performed after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection.

(g) Response assessments for DLBCL per both the modified 2007 IWG response criteria for malignant lymphoma [16] and the 2014 IWG (Lugano) criteria [15], including a CT (with contrast) scan of chest, abdomen, and pelvis (neck should be included, if appropriate) and symptom evaluation, will be performed at Screening; on Days 22-29 (predose) of Cycles 1, 3, and 6; every 3 cycles through Cycle 24; and every 6 cycles thereafter (until PD or the start of alternative therapy). Patients who discontinue treatment and do not have previously documented radiographic PD will undergo CT and response evaluation at the EOT visit. An FDG-PET scan extending from the neck through the mid thighs will be performed at Screening for all patients enrolled. FDG-PET scans should be conducted at the 3 subsequent response assessments (Cycles 1, 3, and 6) and repeated either at the time of assessment for CR or for recurrence/progression of disease. If the patient has had an appropriate FDG-PET and CT scan performed within 28 days of Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at Screening. Central collection of disease assessment images by the sponsor or designee is required for patients.

(h) Including serious PTEs; see Section 10.2.

(i) TAK-659 will be administered PO QD in 28-day cycles at either 100 mg or a 3-dose-level ramp-up leading to 100 mg QD (60, 80, 100 mg QD) depending on which cohort a patient is assigned (A or B).

(j) The study center staff will check the patient diary versus the patient's supply of TAK-659 tablets to assess compliance.

(k) An ophthalmic exam should be performed at Screening, Cycle 2 Day 1, Cycle 7 Day 1, and every 6 cycles thereafter (±2 weeks), and at EOT. See Section 9.4.14 for details.

(l) A serum β-human chorionic gonadotropin pregnancy test will be performed only for women of childbearing potential during Screening. A urine pregnancy test will be performed predose on Day 1 of all cycles and at the EOT visit, and negative results must be available before the first dose may be administered. If the serum pregnancy test is performed within 3 days before the first dose and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request by an IEC/IRB, or if required by local regulations.

(m) Laboratory assessments can be conducted within 3 days before the scheduled visit, with the exception of PK and pharmacodynamic assessments, unless otherwise noted. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it does not need to be repeated on Cycle 1 Day 1.

(n) Urinalysis samples will be collected predose and analyzed at the site's local laboratory.

(o) Cycle 4 only.

(p) HIV, hepatitis B virus, and hepatitis C virus tests will be performed during Screening. Negative results must be available before the first dose of study drug may be administered.

(q) A plasma sample will be obtained for evaluation of ctDNA at Screening, Cycle 5 Day 1, and at EOT/relapse.

(r) An FFPE tumor block or appropriately stained slides from a fresh biopsy is required. Subjects who undergo tumor biopsies must have adequate platelet function per investigator assessment, an activated partial thromboplastin time and a prothrombin time within the normal range, and no history of excessive bleeding or recent exposure to antiplatelet or anticoagulant therapy (eg, clopidogrel [Plavix] or salicylates [aspirin] in the prior 7 days). If a fresh specimen cannot be obtained without putting the patient at unjustifiable risk, slides prepared from the archival specimen supporting a prior DLBCL diagnosis may be submitted to local pathology review. See Section 9.4.16 for details. These samples will be evaluated for candidate biomarkers predictive of response. Archival tumor tissue is to be collected only from enrolled patients and may be collected and sent to the sponsor after initiation of protocol treatment.

(s) Optional tumor biopsies may be obtained from consenting patients at any time during the study as determined by the investigator when patients have responded or responded and relapsed. Subjects who undergo optional tumor biopsies must have adequate platelet function per investigator assessment, an activated partial thromboplastin time and a prothrombin time within the normal range, and no history of excessive bleeding or recent exposure to antiplatelet or anticoagulant therapy (eg, clopidogrel [Plavix] or salicylates [aspirin] in the prior 7 days).

(t) CCI [redacted]

(u) Blood samples for PK analysis will be collected at time points specified in Table A. The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on PK sample collection days. In addition, the dates and exact times of TAK-659 dosing (from patient diaries) will be recorded in the eCRF for the 2 doses of TAK-659 administered before each PK sample collection day.

(v) Cycle 4 only.

(w) CCI [redacted]

CCI

(x) CCI

(y) CCI

(z) This blood sample collected during Screening will be used for local PCR testing of CMV replication; however, a sample will also be collected for central testing at this time point. The CMV viral load data will be entered in the eCRF along with the local normal range for the assay. Further monitoring of CMV, if indicated, will follow the local standard practice.

Table A PK and Pharmacodynamic Sample Breakdown: Cycle 1 Through Cycle 4 (Stages 1 and 2)

	Cycle 1							Cycles 2		Cycle 3		Cycle 4
	Day 1		Day 8 (PK Only)	Day 15		Day 22		Day 1	Day 15	Day 1	Day 15	Day 1
	PK	Pharmaco-dynamics (a)		PK	Pharmaco-dynamics (a)	PK	Pharmaco-dynamics (a)	PK	PK	PK	PK	PK
Predose (within 1 h before dosing on Cycle 1 Day 1 and immediately before dosing on all other days) (b) (c)	X	X		X	X	X	X	X	X (d)	X	X (d)	X
2-4 h postdose (e)	X			X	X	X	X	X (d)	X (d)	X (d)	X (d)	
At time of clinic visit			X (f)									

PK=pharmacokinetics.
When the timing of a PK, pharmacodynamic, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the blood sample collection.
(a) Pharmacodynamic samples in this table refer to cytokines/chemokines. For peripheral blood immune cell assessments, refer to
(b) On days when predose samples are collected, patients will be instructed to arrive at the clinic in the morning without taking their TAK-659 dose at home. The TAK-659 dose will be administered in the clinic after collection of all predose samples.
(c) The timing of the predose samples on Cycle 1 Days 15 and 22, Cycle 2 Days 1 and 15, Cycle 3 Days 1 and 15, and Cycle 4 Day 1 should be encouraged to occur at approximately the same time as TAK-659 dosing times on previous days to ensure that samples represent trough samples.
(d) For dose titration patients only.
(e) The PK and pharmacodynamic samples should be collected at the same time during the 2-4 hours postdose window.
(f) For the Cycle 1 Day 8 visit, patients will be instructed to take their TAK-659 dose at home before their clinic visit. The PK sample can be collected at any time during the clinic visit. A distribution of clinic visit times across patients is to be encouraged to provide a range of postdose PK sampling times across the study population.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the US FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential patients, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR (Code of Federal Regulations) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions (drug-related AEs) to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance activities relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D IWG Response Criteria for Lymphoma

Response Criteria for Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease.	(a) FDG-avid or PET positive before therapy; mass of any size permitted if PET negative. (b) Variably FDG-avid or PET negative; regression to normal size on CT.	Not palpable, nodules disappeared.	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, IHC should be negative.
PR	Regression of measurable disease and no new sites.	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes. (a) FDG-avid or PET positive before therapy; one or more PET positive at previously involved site. (b) Variably FDG-avid or PET negative; regression on CT.	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.	Irrelevant if positive before therapy; cell type should be specified.
SD	Failure to attain CR/PR or PD.	(a) FDG-avid or PET positive before therapy; PET positive at prior sites of disease and no new sites on CT or PET. (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT.		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir.	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than 1 node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive before therapy.	>50% increase from nadir in the SPD of any previous lesions.	New or recurrent involvement.

Source: Cheson BD, et al, 2007 [16].
SD=stable disease, SPD=sum of the product of the diameters.

Appendix E ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, et al [19].

Appendix F Cockcroft-Gault Equation

For men:

$$\text{Creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For women:

$$\text{Creatinine clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

Source: Cockcroft DW, Gault MH, 1976. [20]

Appendix G Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (1):
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation (1):
  - Oral.
  - Injectable.
  - Implantable (2).
- Intrauterine device (IUD) (2).
- Intrauterine hormone-releasing system (IUS) (2).
- Bilateral tubal occlusion (2).
- Vasectomised partner (2) (3).
- Sexual abstinence (4).

Methods That are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide (5).
- Cap, diaphragm, or sponge with spermicide (5).

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

(1) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

(2) Contraception methods that in the context of this guidance are considered to have low user dependency.

(3) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.

(4) In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

(5) Male condom combined with either cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered an acceptable, but not highly effective, birth control method.

Appendix H New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association, 1994 Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix I Medications, Supplements, and Food Products that are Strong CYP3A and/or P-gp Inhibitors or Inducers

Medication, Supplement, or Food Product (a) (b)	Required Washout Period Before First Dose
Strong CYP3A Reversible Inhibitors and/or P-gp Inhibitors	
amiodarone	5 times the inhibitor half-life (if a reasonable half-life estimate is known), or 7 days (if a reasonable half-life estimate is unknown)
azithromycin	
captopril	
carvedilol	
cyclosporine	
diltiazem	
dronedarone	
erythromycin	
felodipine	
ketoconazole	
itraconazole	
nefazodone	
posaconazole	
quercetin	
quinidine	
ranolazine	
ticagrelor	
verapamil	
voriconazole	
Strong CYP3A Mechanism-Based Inhibitors	
clarithromycin (c)	7 days, or 5 times the inhibitor half-life, whichever is longer
conivaptan (c)	
mibefradil (c) (d)	
telithromycin	
grapefruit and grapefruit-containing foods and beverages	5 days
Strong CYP3A Inducers and/or P-gp Inducers	
avasimibe (e)	7 days, or 5 times the inducer half-life, whichever is longer
carbamazepine	
phenobarbital	
phenytoin	
primidone	
rifabutin	
rifapentine	
rifampin	
St. John's wort	

Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

(a) Note that the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the US FDA draft guidance for DDI studies. If a medication, supplement, or food/beverage is suspected or known to be a P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list, then its use must be discussed on a case-by-case basis with the medical monitor or designee to assess the relative benefit and risk.

(b) Note that medications used to treat HIV or hepatitis C infection that are strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.

(c) Also inhibitor of P-gp.

(d) Withdrawn from the US market for safety reasons.

(e) Not marketed in the United States.

Appendix J Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the major changes in Amendment No. 02 are indicated below. Please note that text in Section 2.0 STUDY SUMMARY has also been amended accordingly, but is not described in this Appendix.

Change 1: The IND number, amendment history, and summary of changes were added to the protocol.

Amended or new wording on the Title Page:

Study Number:	C34004		
IND Number:	**119,231**	**EudraCT Number:**	2016-003716-12
Compound:	TAK-659		
Date:	~~14 November 2017~~ **24 April 2018**	**Version/Amendment Number:**	~~01~~**02**

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
27 February 2017	Initial version	Not applicable	Global
14 November 2017	01	Not applicable	Global
24 April 2018	**02**	**Not applicable**	**Germany-specific**

New wording in Section 1.3 and Appendix J:

1.3 Protocol Amendment 02 Summary of Changes

This section describes the changes in reference to the Protocol Incorporating Amendment 02.

Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix J. The following is a summary of the major changes made in the amendment:

Changes in Amendment 02

1. **The IND number, amendment history, and summary of changes were added to the protocol.**
2. **The names of the sponsor's signatories were updated.**
3. **National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version was updated from version 4.03 to version**

5.0.

4. **Definitions of childbearing potential and highly effective contraception methods for female patients of childbearing potential were added to the protocol.**
5. **Definitions of highly effective contraception methods for male patients who are sexually active with partners of childbearing potential were added to the protocol.**
6. **A new inclusion criterion was added and the precautions and restrictions section was revised to state that male patients should not donate sperm from the time of signing the informed consent through 180 days after last dose of study drug.**
7. **One new exclusion criterion was added to exclude patients with known hypersensitivity reactions to the active substance or to any of the excipients of the study drug.**
8. **Suspected pneumonitis was specifically added to all Grade 3 and Grade 4 nonhematologic toxicities.**
9. **A urine pregnancy test for all women of childbearing potential was added to the end of treatment visit.**
10. **Reasons for discontinuation of treatment with study drug were revised.**
11. **Reasons for withdrawal of patients from the study were revised.**
12. **Reasons for early discontinuation of the study by the sponsor were added to the protocol.**
13. **Human immunodeficiency virus (HIV), hepatitis B, and hepatitis C virus tests were added during the Screening period.**
14. **Fresh tumor biopsy criteria were revised.**
15. **Optional tumor biopsy criteria were revised.**

Rationale for Change:

Compliance with Takeda writing guidelines.

Change 2: The names of the sponsor's signatories were updated.

New wording in Section 1.2:

PPD

Date

PPD

Date

Rationale for Change:

Change was made to reflect the addition of the sponsor's new Medical Monitor and new Statistical Lead.

Change 3: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version was updated from version 4.03 to version 5.0.

Amended wording in Sections 6.1, 8.2.1, 10.1.3, 10.2:

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), ~~Version 4.03 14 June 2010~~ **version 5.0, effective date 27 November 2017** [17].

Rationale for Change:

Change was made at the request of the BfArM.

Change 4: Definitions of childbearing potential and highly effective contraception methods for female patients of childbearing potential were added to the protocol.

Revised wording in Section 7.1 (inclusion criterion #10):	10. Female patients ~~who~~ **of childbearing potential must**: ~~a) Are postmenopausal for at least 1 year before the screening visit, OR~~ ~~b) Are surgically sterile, OR~~ **a**) ~~If they are of childbearing potential, a~~**A**gree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the time of signing the informed consent form (ICF) through 180 days after the last dose of study drug, ~~or~~ **OR** **b**) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.) **Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy, or not being postmenopausal for at least 1 year before screening visit (≥12 months of amenorrhea in the absence of other biological or physiological causes).**

Revised wording in Section 8.4:

Nonsterilized female patients of ~~reproductive age~~ **childbearing potential** and male patients should use **highly** effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients **of childbearing potential** must ~~meet 1 of the following:~~

- ~~Postmenopausal for at least 1 year before the Screening visit, OR~~
- ~~Surgically sterile, OR~~
- ~~If they are of childbearing potential,a~~**A**gree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the time of signing of the ICF through 180 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy, or not being postmenopausal for at least 1 year before screening visit (≥ 12 months of amenorrhea in the absence of other biological or physiological causes).

Rationale for Change:

Change was made at the request of the BfArM.

Change 5: Definitions of highly effective contraception methods for male patients who are sexually active with partners of childbearing potential were added to the protocol.

Amended wording in Section 7.1 (inclusion criterion #11):

11. Male patients, even if surgically sterilized (ie, status postvasectomy), who~~:~~ **are sexually active with partners who are of childbearing potential, must:**

    ~~a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, OR~~

    a) Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time from the time of signing the informed consent form (ICF) through 180 days after the last dose of study drug, OR

    b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Amended wording in Section 8.4:

Male patients, even if surgically sterilized (ie, status postvasectomy)**, who are sexually active with partners who are of childbearing potential,** must**:** ~~agree to 1 of the following:~~

- ~~Practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, OR~~
- **Agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method (see Appendix G) at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug, OR**
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Rationale for Change:

Change was made at the request of the BfArM.

Change 6: A new inclusion criterion was added and the precautions and restrictions section was revised to state that male patients should not donate sperm from the time of signing the informed consent through 180 days after last dose of study drug.

New wording in Section 7.1 (inclusion criterion #12) and Section 8.4:	**12. Male patients should not donate sperm from the time of signing the ICF through 180 days after the last dose of study drug.**

Rationale for Change:

Change was made at the request of the BfArM.

Change 7: One new exclusion criterion was added to exclude patients with known hypersensitivity reactions to the active substance or to any of the excipients of the study drug.

New wording in Section 7.2 (exclusion criterion #4)	**4. Known hypersensitivity reactions to the active substance or to any of the excipients of the study drug.**

Rationale for Change:

Change was made at the request of the BfArM.

Change 8: Suspected pneumonitis was specifically added to all Grade 3 and Grade 4 nonhematologic toxicities.

Amended wording in Table 8.c.	**Criteria** **All Grade 3 nonhematologic toxicities, including suspected pneumonitis, with the exception of:** … **Criteria** **All Grade 4 nonhematologic toxicities, including suspected pneumonitis, with the exception of:** …

Rationale for Change:

Change was made at the request of the BfArM.

Change 9: A urine pregnancy test for all women of childbearing potential was added to the end of treatment visit.

New wording in Section 9.4.8 and Schedule of Events, including footnote (l)

9.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine pregnancy test will be performed predose on Day 1 of all cycles **and at the EOT visit**, and negative results must be obtained before the first dose of study drug may be administered. If the screening serum test is done within 3 days before the first dose of study drug in Cycle 1 and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request by an IEC/IRB, or if required by local regulations.

Schedule of Events

(l) A serum beta-human chorionic gonadotropin pregnancy test will be performed only for women of childbearing potential at Screening. A urine pregnancy test will be performed predose on Day 1 of all cycles **and at the EOT visit**, and negative results must be available before the first dose may be administered. If the serum pregnancy test is performed within 3 days before the first dose and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request by an IEC/IRB, or if required by local regulations.

Rationale for Change:

Change was made at the request of the BfArM.

Change 10: Reasons for discontinuation of treatment with study drug were revised.

Amended wording in Section 9.7

9.7 Discontinuation of Treatment With Study Drug ~~and Patient Replacement~~

Treatment with study drug ~~may~~ **must** be discontinued for any of the following reasons:

- ~~AE, including patients who experience toxicity during the first cycle, patients with Grade 4 nonhematologic toxicity, and patients with Grade 4 anemia.~~
- ~~Protocol deviation.~~
- ~~Progressive disease.~~
- ~~Symptomatic deterioration (at investigator's discretion).~~
- ~~Unsatisfactory therapeutic response.~~
- ~~Initiation of hematopoietic stem cell transplant.~~
- ~~Study terminated.~~
- ~~Withdrawal by patient.~~
- ~~Lost to follow-up.~~
- ~~Other.~~
- **Occurrence of drug-related Grade 4 nonhematologic toxicity or Grade 4 anemia, or other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 8.2.**
- **If dosing of TAK-659 is interrupted for >21 days for study drug-related or possibly related AEs despite supportive treatment per standard clinical practice. (Exceptions to this criterion may be made after discussion and agreement between the investigator and the sponsor based on the benefit and risk assessment).**
- **If more than 2 dose reductions are required for a patient.**
- **Occurrence of AEs, resulting in discontinuation of study drug that is desired or considered necessary by the investigator and/or the patient (if applicable).**
- **Disease progression per 2007 and/or 2014 IWG criteria as determined by the investigator (see Section 9.4.15).**
- **Use of a nonpermitted concomitant drug, as defined in Section 8.3, in which the predefined consequence is withdrawal from treatment. (The sponsor should be contacted to discuss whether trial treatment must be discontinued.)**

- **Occurrence of pregnancy (if applicable).**
- **Symptomatic deterioration (at investigator's discretion).**
- **Initiation of hematopoietic stem cell transplant.**
- **Withdrawal of consent by patient.**
- **Patient is lost to follow-up.**

…

Rationale for Change:

Change was made at the request of the BfArM.

Change 11: Reasons for withdrawal of patients from the study were revised.

Amended wording in Section 9.8

9.8 Withdrawal of Patients From Study

Patients may discontinue the trial at any time without giving a reason(s).

A patient ~~may~~ **must** be withdrawn from the study for any of the following reasons:

- ~~AE.~~
- ~~Protocol violation.~~
- ~~Progressive Disease.~~
- ~~Symptomatic deterioration (at investigator's discretion).~~
- ~~Unsatisfactory therapeutic response.~~
- Initiation of hematopoietic stem cell transplant
- ~~Study terminated by sponsor.~~
- Withdrawal **of consent** by patient.
- **Participation in any other therapeutic trial during the treatment duration of this trial.**
- **Patient noncompliance with protocol.**
- ~~Lost to follow-up.~~
- ~~Other.~~

~~The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.~~

Rationale for Change:

Change was made at the request of the BfArM.

Change 12: Reasons for early discontinuation of the study by the sponsor were added to the protocol.

New wording in Section 9.9

9.9 Early Discontinuation of the Study

The sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- **The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.**
- **Poor enrollment of patients, making completion of the trial within an acceptable timeframe unlikely.**
- **Plans to modify or discontinue the development of the study drug.**

The sponsor will notify the investigator if the sponsor decides to discontinue the study.

Rationale for Change:

Change was made at the request of the BfArM.

Change 13: Human immunodeficiency virus (HIV), hepatitis B, and hepatitis C virus tests were added during the Screening period.

New wording in Schedule of Events, including footnote (p)

(p) HIV, hepatitis B virus, and hepatitis C virus tests will be performed during Screening. Negative results must be available before the first dose of study drug may be administered.

Rationale for Change:

Change was made at the request of the BfArM.

Change 14: Fresh tumor biopsy criteria were revised.

New wording in Schedule of Events, including footnote (r)	(**r**)	An FFPE tumor block or appropriately stained slides from a fresh biopsy is required. **Subjects who undergo tumor biopsies must have adequate platelet function per investigator assessment, an activated partial thromboplastin time and a prothrombin time within the normal range, and no history of excessive bleeding or recent exposure to antiplatelet or anticoagulant therapy (eg, clopidogrel [Plavix] or salicylates [aspirin] in the prior 7 days).** If a fresh specimen cannot be obtained without putting the patient at unjustifiable risk, slides prepared from the archival specimen supporting a prior DLBCL diagnosis may be submitted to local pathology review. See Section 9.4.16 for details. These samples will be evaluated for candidate biomarkers predictive of response. Archival tumor tissue is to be collected only from enrolled patients and may be collected and sent to the sponsor after initiation of protocol treatment.

Rationale for Change:

Change was made at the request of the BfArM.

Change 15: Optional tumor biopsy criteria were revised.

New wording in Schedule of Events, including footnote (s)	(**s**)	Optional tumor biopsies may be obtained from consenting patients at any time during the study as determined by the investigator when patients have responded or responded and relapsed. **Subjects who undergo optional tumor biopsies must have adequate platelet function per investigator assessment, an activated partial thromboplastin time and a prothrombin time within the normal range, and no history of excessive bleeding or recent exposure to antiplatelet or anticoagulant therapy (eg, clopidogrel [Plavix] or salicylates [aspirin] in the prior 7 days).**

Rationale for Change:

Change was made at the request of the BfArM.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Apr-2018 18:06 UTC
	Clinical Approval	25-Apr-2018 19:42 UTC
	Clinical Pharmacology Approval	26-Apr-2018 01:13 UTC
	Clinical Approval	26-Apr-2018 18:29 UTC