Title: A Phase 1, Open-label Study of TAK-659 as a Single Agent in Adult East Asian Patients with Non-Hodgkin Lymphoma

NCT Number: NCT03238651

Protocol Approve Date: 6 December 2018

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

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PROTOCOL

A Phase 1, Open-label Study of TAK-659 as a Single Agent in Adult East Asian Patients With Non-Hodgkin Lymphoma

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA USA 02139
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: C34007

Compound: TAK-659

Date: 6 December 2018 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Region
7 March 2017	Initial Protocol	Global
24 May 2017	01	Global
6 December 2018	02	Global

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

Takeda sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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	Contact
Serious adverse event and pregnancy reporting	See Section 10.2
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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 Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): 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

Date

Date

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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for 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 (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

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)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02.

The primary purpose of this amendment is to add 2 possible new cohorts (40 mg QD continuous and 80 mg QD 7 days on/7 days off intermittent regimen) to the dose escalation part, and to change the target tumor type for the expansion part from diffuse large B-cell lymphoma (DLBCL) to follicular lymphoma (FL) or marginal zone lymphoma (MZL). Schedule of Events is revised and new Tables added for this purpose.

Rationales for these changes made are shown below.

1.3.1 Rationale for Addition of the New Cohorts

While encouraging single-agent TAK-659 clinical benefit has been observed in global clinical studies, the durability of the clinical benefit has been limited by toxicities that have led to study treatment interruption and/or discontinuation. In Western population studies, the highest dose of TAK-659 evaluated in the first in human lymphoma study (C34001) in a 28-day cycle was 120 mg/day and the MTD was 100 mg QD. A 7 days on/7 days off intermittent dose of TAK-659 at 60 mg QD in combination with venetoclax at 400 mg QD (study C34008) has been tested without dose-limiting toxicity (DLT). Within study C34007, the starting dose of 60 mg QD was evaluated and one DLT was observed in 6 subjects within Cycle 1, therefore the dose was escalated to 80 mg QD. As of 15 October 2018, 2 patients at 80 mg QD experienced DLTs, one case of Grade 3 febrile neutropenia and Grade 3 hypophosphatemia occurred 2 weeks after initiation of TAK-659 treatment and one case of prolonged asymptomatic Grade 3 amylase/lipase elevations 1 week after dosing TAK-659; therefore 60 mg QD has been considered the MTD for the continuous dosing regimen. However, dose interruptions were frequently experienced throughout treatment cycles. In order to explore optimal dosing regimen for durable long-term tolerability, 2 additional cohorts may open: 40 mg QD continuous (this regimen is considered permissible per protocol amendment 01) and 80 mg QD 7 days on/7 days off intermittent regimen. An alternative intermittent regimen (eg, 60 mg QD 7 days on/7 days off) may be evaluated if deemed necessary per the emerging data. Based on prior experiences, some of the toxicities (eg, creatine kinase elevation) seem to be reversible 1 week after treatment interruption. It is therefore hypothesized a greater benefit/risk ratio may be derived from an intermittent dosing regimen of TAK-659 in patients with lymphoma. This is further supported by the recent approval of copanlisib with once weekly dosing regimen that seemed to have presented a favorable benefit/risk profile in comparison against idelalisib with a twice daily continuous dosing regimen. It is noted that some other B-cell receptor (BCR) inhibitors are also being tested in intermittent dosing regimens, suggesting a drug holiday may not necessarily diminish the efficacy of a BCR pathway inhibitor. Collectively, the sponsor considers plausible to propose the 2 cohorts in dose escalation phase. The recommended phase 2 dose (RP2D) for East Asian patients will be selected among 60 mg QD, 40 mg QD, and 80 mg QD, 7 days on/7 days off regimens or its alternative regimen,

based on the aggregate data of safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and clinical efficacy.

1.3.2 Rationale for Changing the Tumor Type in Expansion Cohort

The early signal from TAK-659 studies directed further development in DLBCL, hence the expansion cohort of this study was planned to focus on DLBCL. However, the phase 2 data of single-agent TAK-659 did not corroborate the early finding in DLBCL. A significant level of objective response (82% in response evaluable population) was observed in patients with FL treated with TAK-659 single agent in the first in human study. However, the durability of the objective response in FL has not been optimal, possibly due to dose modifications associated with the toxicities. With the attempt to optimize the dosing regimen, it is hypothesized that a sustainable long-term dosing of TAK-659 may offer a potential for clinical success in FL. As an indolent disease, FL is a preferred tumor type to test long-term safety profile of TAK-659. Enrollment of MZL, another indolent NHL is allowed to mitigate the concern of undue delay of accrual.

A summary of the other major changes made in the amendment are shown below. Minor grammatical, editorial, formatting and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only. For specific descriptions of text changes and where the changes are located, see Appendix J.

1. Revised the planned number of sites.
2. Updated the diseases under study section to include FL and MZL.
3. Added a sentence to the nonclinical experience section to instruct the reader to refer to the TAK-659 IB for detailed discussion of the nonclinical toxicology, metabolism, and pharmacology of TAK-659.
4. Updated the clinical experience section with more recent data.
5. Updated the risks and benefits section with more recent data.
6. Revised the rationale for the proposed study.
7. Revised the rationale for dose and dosing schedule.
8. Revised the rationale for PK assessments section.
9. CCI [redacted]
10. Revised target tumor type description in the secondary objective regarding evaluation of the preliminary efficacy of TAK-659.
11. CCI [redacted]
12. Revised the assessment time points for the PK-related primary/additional endpoints.
13. Revised the name of the expansion part, and removed one of the secondary endpoints regarding the assessment of time to progression (TTP).

14. Removed response data collection assessed using the IWG 2014 (Lugano) criteria.
15. R[redacted]
16. Revised the overview of study design.
17. Revised the number of subjects to be enrolled into this study.
18. Revised the end of study/study completion definition and planned reporting section.
19. Revised maximum time frames for the primary/secondary endpoints.
20. Revised the total study duration.
21. Revised inclusion criterion #3.
22. Revised inclusion criterion #6.
23. Revised exclusion criterion #9.
24. Revised study drug administration section.
25. Clarified the definitions of DLT.
26. Updated the dose escalation rules section.
27. Added a table showing dose reduction levels for TAK-659.
28. Updated the criteria for beginning or delaying a subsequent treatment cycle.
29. Clarified that the use of excluded medications to manage AEs will require appropriate washout period before resuming the study drug.
30. Added that females cannot donate ova and males cannot donate sperm for 180 days after the last dose of study drug.
31. Added monitoring and prophylaxis procedures for cytomegalovirus (CMV).
32. Added CMV tests to be done at screening and monitored throughout the study.
33. Removed the text describing central reading of radiographic images.
34. Revised the instructions for performing CT scans for disease assessment in the expansion part.
35. Revised the tumor specimen measurements section.
36. Added and reorganized tables indicating the PK, ECG, and pharmacodynamic assessment schedules for the dose escalation part and the expansion part in Appendix A.
37. Added description on the blood sample collection time points for PK for subjects on the new Dosing Schedule B (7 days on/7 days off intermittent dosing).
38. Added a new section for blood sample collection for assessment of the pharmacodynamic effects of TAK-659 on circulating immune cells.
39. Pregnancy was added to the reasons for discontinuation of treatment with study drug.

40. Pregnancy was added to the reasons for withdrawal of patients from study.
41. Revised the posttreatment follow-up assessments section.
42. Revised the PK analysis section.
43. CCI [redacted]
44. Revised Table 13.a (Probabilities of Observing the Minimum Number of Responders Given True Response Rates, Assuming a Total of 12 Response-Evaluable Patients).
45. Updated the protocol deviations section.
46. Updated the IRB and/or IEC approval section.
47. Revised the list of references.
48. Revised to allow predose ECG to be performed outside the 1 hour window before dosing.
49. Clarified that postdose samples for pharmacodynamic assessment (cytokine/chemokine/serum protein) in the dose escalation part and the expansion part, and also the postdose samples for pharmacokinetic assessment in the expansion part should be collected either at 2-hour or 4-hour postdose.
50. Updated the Schedule of Events.

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2.0 STUDY SUMMARY

Clinical Study Sponsor(s): Millennium Pharmaceuticals, Inc	**Compound:** TAK-659	
Study Title: A Phase 1, Open-label Study of TAK-659 as a Single Agent in Adult East Asian Patients With Non-Hodgkin Lymphoma	**IND No.:** Not applicable	**EudraCT No.:** Not applicable
Study Identifier: C34007	**Phase:** 1	

Study Design:

This is an open-label, multicenter, phase 1 study of TAK-659 including a dose escalation part in adult East Asian patients with non-Hodgkin lymphoma (NHL) and an expansion part in adult East Asian patients with relapsed and/or refractory follicular lymphoma (FL) or marginal zone lymphoma (MZL).

The dose escalation part of the study will enroll approximately 18 to 32 East Asian patients diagnosed with NHL for which no effective standard treatment is available. Assuming a dropout rate of 20%, this will ensure that 16 to 28 dose-limiting toxicity (DLT)-evaluable patients are enrolled in the dose escalation part. TAK-659 will be administered continuously, once daily (QD) (Dosing Schedule A), or a 7 days on/7 days off intermittent regimen (Dosing Schedule B) in 28-day treatment cycles. Dose escalation will follow a standard 3+3 schema to determine the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D). The initial TAK-659 dose will be 60 mg QD and will escalate to 80 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses or regimens, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-659. If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of adverse events (AEs)/DLTs observed, and following the examination of the preliminary pharmacokinetic (PK) results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion the investigators and the sponsor. If ≥2 of 6 patients experience a DLT at 80 mg QD, alternate dose regimens between 60 and 80 mg (ie, 80 mg 7 days on 7 days off [Dosing Schedule B]) will be evaluated as described below. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the totality of the safety, tolerability, as well as preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Intrapatient dose escalation is not allowed in this protocol.

An additional dosing schedule will be tested after implementation of Amendment 02:

Dosing Schedule B: TAK-659 will be administered QD for 7 consecutive days followed by another 7 days of rest and repeated again (ie, 7 days "on" and 7 days "off"), for a cycle duration of 28 days. The starting dose of 80 mg QD was the maximum administered dose in Dosing Schedule A (2 out of 4 patients presented a DLT in the continuous dosing regimen). However, the alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data. Dose escalation will be governed using the same standard 3+3 schema.

The expansion part of this study will begin once the RP2D has been determined. The expansion part will proceed with dosing of TAK-659 at the RP2D in 28-day cycles. The patient population will consist of East Asian patients with FL or MZL who are relapsed and/or refractory after at least 2 prior lines of chemotherapy and who must be ineligible for or refusal to hematopoietic stem cell transplant. It is expected that approximately 12 response-evaluable patients will be enrolled. Assuming a 20% dropout rate, a total of approximately 15 patients will be enrolled. The objectives of the expansion part are to evaluate the longer-term safety and tolerability of TAK-659 administered at the RP2D, to characterize the PK of TAK-659, and to evaluate the preliminary efficacy of TAK-659 in relapsed and/or refractory FL or MZL. Disease assessment will be performed according to the International Working Group (IWG) 2007 criteria.

At least 1 Japanese patient will be enrolled in each cohort in the dose escalation part. The total number of Japanese patients dosed at the RP2D (either the MTD or a lower dose as determined) will be at least 6 including the dose

escalation and expansion parts to ensure adequate characterization of PK and safety in Japanese patients.

Intensive PK samples will be collected during Cycle 1 in all patients in the dose escalation part to permit detailed characterization of TAK-659 PK. Sparse PK samples will be collected in expansion patients to contribute to population PK and exposure-response analyses. If fewer than 6 Japanese patients are dosed at the RP2D during dose escalation, additional intensive PK samples will be collected during Cycle 1 in a subset of Japanese patients in the expansion part. In total, intensive PK sampling will be performed in at least 6 Japanese patients dosed at the RP2D.

CCI

On the basis of the geographic distribution of patients enrolled and emerging PK and safety data, additional patients may be added, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region. On the basis of emerging efficacy data, additional groups or patients with FL/MZL may be added to further explore efficacy.

Primary Objectives:

- To determine the safety, tolerability, and MTD and/or RP2D of TAK-659 administered orally QD to East Asian patients with NHL who do not have an effective standard treatment available.
- To characterize the plasma and urine PK of TAK-659 in East Asian patients with NHL.

Secondary Objective:

- To evaluate preliminary efficacy of TAK-659 in patients with relapsed and/or refractory NHL.

CCI

Subject Population:

Dose escalation part: East Asian patients with a diagnosis of histologically or cytologically confirmed NHL, for which no effective standard treatment is available.

Expansion part: East Asian patients with relapsed and/or refractory FL or MZL after at least 2 prior lines of chemotherapy and who must be ineligible for or refusal to hematopoietic stem cell transplant.

Planned Number of Subjects:	**Planned Number of Sites:**
Approximately 33 to 47 patients Dose escalation part: Approximately 18 to 32 patients Expansion part: Approximately 15 patients	Dose escalation part: approximately 3-5 sites Expansion part: approximately 6-10 sites
Dose Level(s): The study drug will be dosed continuously, QD, in 28-day cycles with a starting dose of 60 mg. Dose escalation will follow a standard 3+3 escalation scheme. If 60 mg QD is safe and tolerable, then the dose will be escalated to 80 mg QD. Dose escalation will continue until MTD and/or RP2D is determined. After implementation of Amendment 02: With 80 mg QD having exceeded the MTD and long term tolerability concerns of 60 mg QD, the study has planned to test	**Route of Administration:** Oral

40 mg QD continuous dosing. Further, a 7 days on/7 days off intermittent regimen at 80 mg QD is proposed to explore potentially improved benefit/risk profile. An alternative intermittent regimen (eg, 60 mg QD 7 days on/7 days off) may be evaluated if deemed necessary per emerging data. In the expansion part, TAK-659 will be dosed at the RP2D, QD or the intermittent regimen, in 28-day cycles.	
Duration of Treatment: Patients will receive study drug until disease progression, unacceptable toxicity, or withdrawal due to other reasons. Estimated median treatment duration is 6 months.	**Period of Evaluation:** Safety follow-up: Patients will be followed for safety for approximately 28 days after their last dose of study drug or until the start of subsequent antineoplastic therapy, whichever occurs first. Progression-free survival (PFS) follow-up (in expansion part only): up to 6 months after the last dose of study drug (for patients who discontinue for reasons other than disease progression) or until progression, whichever occurs first. It is anticipated that this study will last for approximately 52 months.

Main Criteria for Inclusion:

- Male or female patients of East Asian ethnicity (eg, Japanese, Korean, or Chinese) aged 18 years or older (if local regulation requires a minimum age for informed consent of more than 18 years, then patients must be the minimum age or older per the local regulation) when written study informed consent is obtained.
- To be enrolled into the dose escalation part, patients must have:
  a) Histologically or cytologically confirmed diagnosis of NHL for which no effective standard treatment is available. However, patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, primary central nervous system (CNS) lymphoma, or Waldenström macroglobulinemia will be excluded.
  b) Radiographically or clinically measurable disease with at least 1 target lesion. Radiographically measurable disease is determined by IWG 2007 criteria for malignant lymphoma.
- To be enrolled into the expansion part, patients must meet the following criteria:
  a) Patients must have pathologically confirmed FL (Grade 1, 2, or 3A) or MZL.
  b) Relapsed and/or refractory to ≥2 prior lines of chemotherapy based on standard of care that include at least 1 anti-CD20-based regimen, as well as alkylating agents (eg, cyclophosphamide or bendamustine).
  c) Patients must be ineligible for or refusal to hematopoietic stem cell transplant.
  d) For patients who have relapsed or progressed after achieving a response (defined as complete response [CR] or partial response [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.
  e) Must have measurable disease that meets the size criteria per IWG (>1.5 cm in the longest diameter for a lymph node or a nodal mass, or >1.0 cm in the longest diameter for an extranodal disease) as assessed on cross-sectional imaging by computed tomography (CT) scan/magnetic resonance imaging (MRI). (CT scan is to be performed with contrast unless it is medically contraindicated.)
- Eastern Cooperative Oncology Group performance status score of 0 or 1.
- Life expectancy of longer than 3 months.
- Patients must have adequate organ function, including the following:

a) Bone marrow reserve: absolute neutrophil count ≥1,000/mm^3, platelet count ≥75,000/mm^3 (≥50,000/mm^3 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 function: total bilirubin ≤1.5×the upper limit of the normal range (ULN); alanine aminotransferase and aspartate aminotransferase ≤2.5×ULN.

c) Renal function: creatinine clearance ≥60 mL/min either as estimated by the Cockcroft-Gault equation.

Main Criteria for Exclusion:

- CNS lymphoma; active brain or leptomeningeal metastases as indicated by positive cytology from lumbar puncture or CT/MRI by local assessment.
- 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 agent; ≤8 weeks for cell-based therapy or anti-tumor vaccine).
- Radiotherapy less than 3 weeks before the first dose of study treatment. If prior radiotherapy occurred <4 to 6 weeks before the study start, as radiated lesions cannot be reliably assessed by FDG-PET, nonradiated target lesions are required for eligibility.
- 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 at any time.
- 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.
- Use or consumption of any of the following substances:
  - 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, the use of these agents is not permitted during the study except for AE management (see Section 8.5 for details).See Appendix I for a nonexhaustive list of strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the United States Food and Drug Administration (FDA) Draft Drug-Drug Interaction (DDI) Guidance.
  - 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, the use of these agents is not permitted during the study except for AE management (see Section 8.5 for details). See Appendix I for a nonexhaustive list of strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the FDA Draft DDI Guidance.
  - Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverage are not permitted during the study.

Main Criteria for Evaluation and Analyses:

Primary:

- Percentage of patients with treatment-emergent AEs (TEAEs).
- Percentage of patients with Grade 3 or higher TEAEs.
- Percentage of patients with serious TEAEs.
- Percentage of patients with DLTs during Cycle 1 (dose escalation part only).
- Percentage of patients discontinuing study drug because of TEAEs.
- Percentage of patients with clinically significant abnormal laboratory values.
- Percentage of patients with clinically significant abnormal vital sign measurements.

- TAK-659 maximum observed concentration (C_{max}) on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 time of first occurrence of Cmax (T_{max}) on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 area under the plasma concentration-time curve during the dosing interval on Cycle 1 Days 1 and 7 or 15 by dose.
- Renal clearance (CL_R) on Cycle 1 Day 7 or 15 by dose.

Secondary:

- Overall response rate in the expansion part.
- CR rate in the expansion part.
- Duration of response in the expansion part.
- PFS in the expansion part.

The investigator will perform response assessment using modified IWG 2007 criteria for malignant lymphoma.

Additional:

- Apparent oral clearance (CL/F), CLR as a percentage of CL/F, peak-trough ratio, accumulation ratio, and observed concentration at the end of the dosing interval on Cycle 1 Day 7 or 15 by dose.
- Plasma concentration-time data contributing to population PK and exposure-response analyses.

CCI

[redacted]

Statistical Considerations:

Analysis for primary endpoints will be descriptive using percentages and summary statistics. For the secondary efficacy endpoints, percentages will be used for binary endpoints, and Kaplan-Meier analysis will be used for time-to-event endpoints.

All statistical analyses will be primarily descriptive in nature. No formal statistical hypothesis testing will be performed. A statistical analysis plan will be developed and finalized before database lock.

Sample Size Justification:

No formal statistical power calculations to determine sample size were performed for this study.

This study will use a standard 3+3 design in the dose escalation part. Approximately 4 dose cohorts (3-6 patients per cohort) are projected, and approximately 16 to 28 DLT-evaluable patients will be enrolled. The actual number of patients may vary depending on the actual doses being tested. Assuming a dropout rate of 20%, the dose escalation part will enroll approximately 18 to 32 patients.

The sample size of approximately 12 response-evaluable subjects for the expansion part has been chosen to permit an adequate assessment of safety and a preliminary assessment of efficacy. Assuming a dropout rate of 20%, the expansion part will enroll approximately 15 patients.

The actual number of patients to be enrolled may increase on the basis of emerging data to allow a sufficient number of PK/safety-evaluable patients per country or East Asian race group or to further assess efficacy in a specific subtype or group of patients with FL or MZL.

At least 1 Japanese patient will be included in each cohort in the dose escalation part, and at least 6 Japanese patients will be evaluated at the RP2D (either the MTD or a lower dose) to ensure adequate characterization of safety and PK in Japanese patients.

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 or equivalent. The identified vendors will perform specific study-related activities will perform these activities either 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, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-HT_3	5-hydroxytryptamine 3 serotonin receptor
ABC	activated B-cell
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
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	area under the plasma concentration-time curve during the dosing interval
BCR	B-cell receptor
BCRP	breast cancer resistance protein
CL/F	apparent oral clearance
CLL	chronic lymphocytic leukemia
CL_R	renal clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
C_{trough}	observed concentration at the end of a dosing interval
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interactions
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
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	fluoro-2-deoxy-D-glucose

FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FL	follicular lymphoma
FLT3	FMS-like tyrosine kinase 3
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
IWG	International Working Group
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
ORR	overall response rate
PBMC	Peripheral blood mononuclear cell(s)
PD	progressive disease (disease progression)

PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PO	per os; by mouth (orally)
PR	partial response
PTR	peak-trough ratio
QD	quaque die; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
Rac	accumulation ratio
RBC	red blood cell
R-CHOP	rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
T_{max}	time of first occurrence of C_{max}
TTP	time to progression
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

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes, or natural killer (NK) cells. Mature B-cell lymphomas account for greater than 85% of NHL cases worldwide. The two most common types of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) [1]. NHL is one of the most common malignancies worldwide, with an estimated 386,000 new cases and 200,000 deaths in 2012. The incidence of NHL exhibits marked geographic variation and is higher in North America and Europe. The East Asia region has one of the lowest incidence rates. While the increasing incidence of malignant lymphoma has recently slowed in Western countries, other parts of the world, including East Asia, have continued to experience an upward trend. In 2012, an estimated 63,000 people in the United States (US), 34,000 people in Western Europe, and 72,000 people in East Asia (21,000 Japanese; 43,000 Chinese; and 4,700 South Korean) were diagnosed with NHL [2].

In East Asia, it is the same tendency with the Western countries that B-cell neoplasms are the most common followed by T/NK cell neoplasms. The proportion of mature B-cell and T/NK cell lymphoma subtypes is different, while the most common subtype is DLBCL in China, Korea and Japan. Japan shows a higher proportion of FL and adult T-cell leukemia/lymphoma cases, and China has a higher proportion of extranodal NK/T-cell lymphoma, nasal type cases [3]. In Korea, precursor cell neoplasms are relatively high and MZL is the second most common subtype among mature B-cell lymphoma [4].

4.1.1.1 DLBCL

DLBCL represents about 30% of all NHL. It is estimated that approximately 20,000; 10,000; 6,400; 12,000; and 1,400 new cases of DLBCL are diagnosed annually in the United States, Western Europe, Japan, China, and South Korea, respectively [2]. DLBCL is a form of aggressive B-cell NHL that is invariably fatal without treatment.

Treatment guidelines in Asia generally follow the National Comprehensive Cancer Network guidelines. Despite slight differences in approved drugs, the systematic therapy pattern for DLBCL in Asia is very similar to that in the United States and Western Europe. The immunochemotherapy regimen R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) is the standard treatment for patients newly diagnosed with DLBCL worldwide. This frontline regimen results in complete response (CR) in approximately 60% to 75% of patients with DLBCL as reported in trials with Western patients [5,6]. In a key publication in Japan, a CR rate of 78% was reported with the frontline R-CHOP regimen in patients with DLBCL [7]. This treatment is considered curative in a subset of patients, with a cure rate of >50% [8,9]. However, DLBCL is highly heterogeneous in histology, clinical

behavior, and underlying biology and therefore exhibits significant variation in outcome after therapy [5,10].

High-dose chemotherapy, including salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), followed by autologous stem cell transplant (ASCT) is 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 these patients. However, clinically meaningful benefit is rarely achieved in patients with progressive disease (PD) following multiple regimens.

Consistent with the heterogeneity in underlying biology, it has been reported that DLBCL can be molecularly subclassified into 3 categories based on gene expression profiles [11]. One of the subtypes, a BCR/proliferation subtype identified in ~40% of DLBCL, has higher expression of BCR signaling components such as CD19, IgH, CD79α, BLK, spleen tyrosine kinase (SYK), PLCγ2, and MAP4K. BCR signaling has subsequently been shown to be a critical driver of tumorigenesis in the BCR subtype of DLBCL. Therefore, inhibition of BCR signaling by a SYK inhibitor such as TAK-659 might generate pronounced antitumor effects in DLBCL, particularly in the BCR-driven subpopulation.

4.1.1.2 Indolent NHL

Follicular lymphoma (FL) is the most common indolent NHL in the Western hemisphere, representing 20% of NHL [12], whereas Asian frequency is different from that of the Western. It varies in each Asian country; 2.9%, 1.7%, 21.7% of total lymphoid neoplasms in China, Korea, Japan [3]. Randomized clinical trials have demonstrated that the addition of rituximab to standard chemotherapy induction has improved overall survival. Maintenance rituximab strategies can improve PFS. Bendamustine combined with rituximab has rapidly become a standard frontline strategy in North America and parts of Europe. However, several unmet needs remain, including the identification of high-risk patients at diagnosis and the development of predictive biomarkers for targeted agents [12].

Other common B cell malignancies include Mantle cell lymphoma (MCL) and MZL. These B cell lymphoma subtypes comprise about 6% and 10% of all NHL respectively [13]. In Asia, the proportion of MCL and MZL is 2.4%, 8.3% in China, 1.8%, 13.5% in Korea and 3.3%, 4.3% in Japan of total lymphoid neoplasms [3]. MCL is poor prognostic despite the development of therapeutic strategy based on understanding of its biology and is thought to have the worst characterstics of both indolent and aggressive NHLs [14]. MZL is heterogeneous and clinocopathological subtypes are extranodal MZL of MALT, nodal MZL and splenic MZL[13].

For indolent B-NHL, watchful wait or radiotherapy is frequently used for early stage or low-tumor burden lymphoma, while rituximab or rituximab plus cytotoxic agent(s) such as CHOP, bendamustine is administered for patients who require chemotherapy [15,16]. In Japan, R-CHOP or R-Bendamustine is frequently chosen as the frontline treatment for FL and MZL [17-19]. In

relapsed or refractory iNHL, bendamustine as a single agent or rituximab-containing chemotherapy regimens can be used.

In Korea, R-CVP (cyclophosphamide, vincristine, prednisolone) is used for MZL [20], and R-CVP and R-CHOP are used for FL [21].

4.1.2 Study Drug

TAK-659, created by Takeda Pharmaceutical Company Limited, is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FMS-like tyrosine kinase 3 (FLT3) and is currently under development for the treatment of patients with advanced malignancies. Dual SYK/FLT3 inhibition represents a novel mechanism of action, and currently there are no marketed drugs with either a dual SYK/FLT3 or SYK alone mechanism of action.

SYK is a nonreceptor protein tyrosine kinase that is widely expressed in hematopoietic cells. It is involved in coupling activated immune receptors to downstream signaling pathways that mediate diverse cellular responses, including proliferation, differentiation, and survival. SYK activation leads to phosphorylation and subsequent activation of a number of downstream signaling pathways (eg, PI3K, MAPK, and NF-κB). The SYK pathway is implicated in hematologic tumors and select solid tumors (eg, Epstein-Barr virus [EBV]-mediated nasopharyngeal tumors).

FLT3 is a receptor tyrosine kinase that plays a role in hematopoiesis. Activating mutations in tyrosine kinase genes, including FLT3, are found in approximately 30% of patients with de novo acute myelogenous leukemia (AML). Mutations in the FLT3 gene most often involve internal tandem duplication of the juxtamembrane domain coding region or point mutations of the tyrosine kinase domain, resulting in ligand-independent proliferation due to constitutive activation of the FLT3 receptor, conferring poor prognosis for patients.

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. 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

In vitro and in vivo pharmacology studies demonstrated that TAK-659 is a potent, reversible SYK and FLT3 inhibitor. TAK-659 has exhibited significant antitumor activity in a number of mouse DLBCL xenograft models, including the OCI-Ly10 model, an activated B-cell-like (ABC)-DLBCL model; the OCI-Ly19 model, a germinal center B-cell–like (GCB)-DLBCL model; the PHTX-95L model, a primary human DLBCL model; the TMD8 ABC-DLBCL model; the RL follicular lymphoma (FL) model; and the MINO mantle cell lymphoma (MCL) model. In nonclinical species, TAK-659 has good oral bioavailability, low plasma protein binding, moderate to large volumes of distribution, and moderate to high plasma clearance. The TAK-659 nonclinical

pharmacokinetic (PK) profile makes it a suitable candidate for clinical development. On the basis of results of nonclinical safety pharmacology studies, TAK-659 is not expected to cause cardiovascular (CV), respiratory, or central nervous system (CNS) effects in patients. Overall, the nonclinical safety profile of TAK-659 has been adequately characterized. The nonclinical assessment of TAK-659 supports clinical trials in patients with advanced malignancies such as relapsed and/or refractory FL.

A detailed discussion of the nonclinical toxicology, metabolism, and pharmacology of TAK-659 can be found in the TAK-659 IB.

4.1.4 Clinical Experience

4.1.4.1 Clinical Experience with TAK-659

TAK-659 is being investigated in 7 clinical studies involving patients with advanced malignancies (Table 4.a) in addition to this study. The status of each study is described below.

Currently, more than 300 patients have been dosed with TAK-659, including 143 patients in first-in-human (FIH) Study C34001 (single-agent study in advanced solid tumors and lymphomas), 43 patients in Study C34002 (single-agent study in relapsed or refractory AML), 41 patients in Study C34003 (study of TAK-659 in combination of nivolumab in advanced solid tumors), 49 patients in Study C34004 (single-agent study in DLBCL), 41 patients in Study C34005 (study of TAK-659 in different combinations in NHL), 10 patients in Study C34007 (single-agent dose escalation study in Japanese patients), and 11 patients in Study C34008 (study of TAK-659 in combination with venetoclax in NHL). Further details about safety and efficacy on these clinical studies are provided in the current IB.

For detailed clinical study information, please refer to the TAK-659 IB.

Table 4.a Overview of TAK-659 Clinical Studies

Protocol No. / Status	Study Design and Population	Dosing Regimen
C34001/ Closed to enrollment	Open-label, multicenter, phase 1, dose escalation study of TAK-659 in adult patients with advanced solid tumors and lymphoma malignancies	Increasing TAK-659 oral doses of 60, 80, 100, and 120 mg QD during dose escalation; MTD of 100 mg QD further explored in patients with lymphoma during dose expansion.
C34002/ Closed to enrollment	Open-label, multicenter, phase 1b/2, dose escalation study of TAK-659 in adult patients with relapsed or refractory AML	Starting TAK-659 dose of 60 mg QD; additional doses of 100, 120, 140, and 160 mg QD; 60 mg BID and 80 mg BID evaluated; QD MTD is 160 mg; BID MTD is 60 mg BID.
C34003/ Closed to enrollment	Open-label, multicenter, phase 1b, dose escalation and dose expansion study of TAK- 659 in combination with nivolumab in adult patients with advanced solid tumors.	TAK-659: starting dose of 60 mg QD; dose has been escalated to 100 mg QD. RP2D will be used in expansion cohorts. Nivolumab: 3 mg/kg IV dosing over 60 min Q2W (Days 1 and 15 of each 28-day cycle). If the 240 mg fixed dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg. MTD of TAK-659 80 mg QD further explored in Triple Negative Breast Cancer patients in expansion
C34004/ Ongoing	Open-label, multicenter, phase 2 study in adult patients with relapsed or refractory DLBCL, beginning with a lead-in dose exploration phase with 2 TAK-659 dose regimens	Cohort 1: TAK-659 100 mg QD in 28-day treatment cycles Cohort 2: TAK-659 increasing dose (every 28 days) beginning with 60 mg QD, followed by 80 mg QD, up to 100 mg QD
C34005/ Ongoing	Open-label, multicenter, phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination agents (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with NHL after at least 1 prior line of therapy	TAK-659: starting dose of 60 mg QD; dose will be escalated to 100 mg QD until MTD is reached, assuming tolerability at the lower doses (60, 80 mg QD). *Combination Agents:* (A) Bendamustine: 90 mg/m^2 administered IV over 10 or 60 min (depending on which formulation is used) on Days 1 and 2 of each 21-day cycle, up to 8 cycles (B) Bendamustine + rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 min (depending on which formulation is used) on Days 1 and 2 of each 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab IV on Day 1 of each 21-day cycle, up to 8 cycles (C) Gemcitabine: 1000 mg/m^2 IV infusion over 30 min on Days 1 and 8 of each 21-day cycle (D) Lenalidomide: 25 mg PO QD for Days 1-21 of each 28-day cycle (E) Ibrutinib: 560 mg PO QD of a 28-day cycle Currently Arms A, C, D, E have been closed. TAK-659 + bendamustine +rituximab will be further explored in FL or MZL patients only.

Footnotes are on last table page.

Table 4.a Overview of TAK-659 Clinical Studies(Continued)

Protocol No. / Status	Study Design and Population	Dosing Regimen
C34008/ Ongoing	Dose escalation phase: adult patients with advanced NHL of any histology. Patients will be refractory or relapsed after at least 1 prior line of therapy with no effective standard therapy available.	TAK-659: 40 mg, 60 mg, 80 mg or 100 mg PO QD, or alternative dosing regimens, as needed, such as intermittent TAK-659 for 7 days on followed by 7 days off, or 14 days on followed by 7 days off, plus one of the following venetoclax regimens administered in 28-day cycles after Cycle 1 (35 days): • 50 mg QD increasing to 200 mg QD by Day 16. • 50 mg QD increasing to 400 mg QD by Day 17. • 50 mg QD increasing to 800 mg by Day 19.
C34015/ Planned	A phase 1b study of TAK-659 in combination with NKTR-214 in patients with advanced NHL after 2 but no more than 3 prior lines of therapy	TAK-659: starting dose of 60 mg QD; 80 mg QD or 100 mg QD, or alternative dosing regimens, as needed, such as intermittent dosing in a 21 day cycle NKTR-214: 0.003 mg/kg or 0.006 mg/kg IV dosing over 30 min on Day 1 of each 21 day cycle). MTD or RP2D of TAK-659 with NKTR-214 will be investigated in expansion.

AML=acute myeloid leukemia, BID=twice daily, DLBCL=diffuse large B-cell lymphoma, IV=intravenous, MTD=maximum tolerated dose, NHL=non-Hodgkin lymphoma, PO=oral(ly), Q2W=every 2 weeks, QD=once daily, RP2D=recommended phase 2 dose.

4.1.4.2 Clinical PK of TAK-659

Preliminary plasma pharmacokinetics (PK) results are available from lymphoma, solid tumor, and AML patients enrolled in Studies C34001 and C34002. In addition, preliminary urine PK results are available from lymphoma and solid tumor patients enrolled in the dose escalation cohorts of Study C34001. TAK-659 is characterized by fast absorption (overall median T_{max} [time of first occurrence of C_{max} (maximum observed concentration)] of 2 hours) in patients with hematologic and nonhematologic malignancies. Moderate variability is observed among dose-normalized steady-state AUC_{τ} (area under the plasma concentration-time curve during the dosing interval) values in lymphoma, solid tumor, and AML patients (coefficient of variation of 20.0%, 43.5%, and 34.8%, respectively). An approximately dose-proportional increase in steady state AUC_{τ} was observed over the 60 to 160 mg range in patients with AML. Mean accumulation ratios ranging from 1.90-fold to 2.54-fold and mean peak-to-trough ratios ranging from 4.34 to 5.09 were observed across the study populations after repeated QD dosing for 15 days. Based on data in lymphoma and solid tumor patients, renal clearance accounted for about 30% of TAK-659 apparent clearance, and therefore at least about 30% of TAK-659 systemic clearance. Active tubular secretion appeared to be the predominant component of renal clearance, based on comparison of unbound renal clearance to glomerular filtration rate. Geometric mean terminal disposition half-life of 34.4 hours was determined in a single dose PK run-in phase of the indolent NHL expansion cohort of Study C34001.

Refer to the TAK-659 IB for detailed clinical pharmacology information.

4.1.5 Risks and Benefits

Because TAK-659 has been administered to limited number of patients, it is not currently possible to identify and describe with certainty the adverse effects of the compound.

4.1.5.1 Potential Risks Identified From Nonclinical Studies

Potential risks from nonclinical studies in dogs and rats include:

- 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/or 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 Based on Clinical Observations

As of the 22 October 2017 data cutoff, following evaluation of the current safety data, asymptomatic lipase elevation, pneumonitis, and infections (including pneumonia, CMV infections, and sepsis) are recognized as potential risks.

Asymptomatic Lipase Elevation

In clinical studies to date, lipase elevations are reported commonly (≥10%). Patients in study C34007 will have frequent monitoring of lipase and amylase as outlined in the Schedule of Events (Appendix A).

Pneumonitis

Cases of pneumonitis have been reported in clinical studies with B-cell receptor (BCR) pathway kinase inhibitors, including TAK-659, and pneumonitis is considered a potential risk of TAK-659. There were 5 SAEs of pneumonitis (4 reported in C34001 and 1 reported in C34002). Pneumonitis and other pulmonary toxicities are being closely monitor patients for respiratory signs and symptoms throughout TAK-659 treatment.

Infections

In an analysis of safety data from 107 patients with lymphoma treated with single-agent TAK-659 in Study C34001, most patients (72%) experienced at least 1 TEAE of any grade classified under the infections and infestations System Organ Class (SOC) as defined by the Medical Dictionary for Regulatory Activities (MedDRA). Pneumonia was the most frequently reported infection TEAE (26%) and most frequently reported infection SAE (15%). CMV infection (20%) and sepsis (17%) were also frequently reported infection TEAEs. Sepsis (17%) and pneumonia (15%) were the most frequently reported ≥ Grade 3 infection TEAEs. In a heavily pretreated relapsed and/or refractory lymphoma patient population, a high rate of infection is expected particularly when considering confounding factors such as comorbidities or other immunosuppressive medications. The rate of infection, including pneumonia and sepsis, observed in patients with lymphoma who received TAK-659 is high and warrants continued monitoring and/or prophylaxis as outlined by this protocol.

Refer to the TAK-659 IB for detailed information on potential risks.

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 indicated (see Section 8.5).

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 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 RNA 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 BCRP in Caco-2 cells at concentrations up to 100 μM. When these in vitro findings are viewed in context of the maximum observed concentration (C_{max}) 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 TAK-659 IB.

4.1.5.4 Potential Benefits Based on Clinical Observations

The benefits of TAK-659 have not been established; however the clinical benefit of TAK-659 has been and continues to be investigated as a single agent or in combination with other agents for the treatment of patients with advanced solid tumors, NHL, and AML. Early signs of clinical antitumor activity were seen.

Clinical benefit has been observed in First In Human Study C34001 evaluating TAK-659 as a single agent. Response data were available for 106 patients (11 solid tumor, 69 DLBCL, 17 iNHL, 5 Chronic Lymphocytic Leukemia [CLL]), 3 Mantle Cell Lymphoma (MCL), and 1 Post Transplant Lymphoproliferative Disorder (PTLD) as of 22 October 2018 in Study C34001. Among response-evaluable patients with solid tumors, 1 patient experienced a partial response (PR). Among response-evaluable patients with DLBCL, best responses of CR and PR were reported for 14 and 12 patients, respectively. Among the 5 response-evaluable patients with CLL, 3 patients achieved PR. Thirteen patients with indolent lymphomas responded to treatment with TAK-659. Four patients achieved a CR and 9 patients achieved PR. These indolent responders were made up of both Follicular and Marginal Zone Lymphoma patients. Lastly, 1 out of 3 patients with MCL achieved a PR.

Additional single agent activity was observed in Studies C34004, a phase 2 R/R DLBCL study and this study, C34007. Of 41 response evaluable DLBCL patients in C34004, 8 responded. Three out of 4 DLBCL and 2 out of 2 FL patients responded in C34007.

Responses have also been observed in two additional NHL studies where TAK-659 was combined with other agents. Fifteen out of 29 response evaluable NHL patients responded in Study C34005, a five-arm combination study with more than half of patients enrolled into the Bendamustine +/- Rituximab arms. Four out of 5 response evaluable NHL patients responded in Study C34008, a Phase 1b study of TAK-659 in combination with venetoclax.

Specific details of the tumor response by cancer type can be found in the TAK-659 IB.

4.2 Rationale for the Proposed Study

This study is intended to evaluate the safety, tolerability, PK, and efficacy of single-agent TAK-659 in East Asian patients with NHL and to expand the TAK-659 global clinical development program to the East Asian population.

The TAK-659 MTD and RP2D in Western patients with lymphoma were determined in the FIH study (C34001) to be 100 mg QD in 28-day treatment cycles. Objective responses have been observed in patients with lymphoma (DLBCL, iNHL [FL and MZL], CLL, and MCL) across the multiple dose levels evaluated (60-120 mg QD), supporting further evaluation of TAK-659 in relapsed and/or refractory FL or MZL after at least 2 prior lines of chemotherapy; a setting that represents an unmet medical need in which there is no standard of care available.

In addition, on the basis of the currently available data, TAK-659 administration can lead to adverse events (AEs) that are generally manageable and reversible with dose modification and/or prophylactic/supportive care. AEs reported in the clinical studies to date are consistent with nonclinical toxicology findings of TAK-659, published studies of other BCR pathway inhibitors [22-24], and the patient population being studied. These events are detectable using standard safety monitoring practices and are generally manageable in the clinical setting.

These results support the initiation of an Asian phase 1 study, including a dose escalation part to determine the MTD and/or RP2D and PK profile of TAK-659 in East Asian patients with NHL and

a dose expansion part to further evaluate the safety and investigate preliminary efficacy in patients with relapsed and/or refractory FL/MZL.

4.2.1 Rationale for Dose and Dosing Schedule

Because this is the first clinical study of TAK-659 in Asia, the initial dose and dose increment will be determined on the basis of the starting dose and MTD from the FIH study (C34001) conducted in Western patients.

Although 100 mg QD TAK-659 has been determined to be the MTD 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 in Western patients, responses to TAK-659 were also observed in patients treated with two lower doses evaluated (60 mg and 80 mg) QD, suggesting a therapeutic window of TAK-659 extending from 60 mg to 100 mg QD. Plasma PK exposure of TAK-659 from that study 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 Western MTD of 100 mg QD and may fall at a QD dose or intermittent schedule below that. It is also possible that there may be efficacious doses below 60 mg QD which is why 40 mg QD will also be tested. In this study, intermittent dosing schedules of TAK-659 will be also be evaluated such as 7 days on followed by 7 days off. The rationale for intermittent dosing schedules for TAK-659 is based on the occurrence of frequent dose interruptions in Cycle 1 and 2 due to various AEs that was observed in study C34001. Most of the AEs that led to drug holds were laboratory changes that returned to ≤Grade 1 with drug hold. In addition to this, most subjects in C34001 that received more than 6 cycles of treatment had multiple dose holds and dose reductions from 100 mg down to 60 mg QD. Moreover, TAK-659 intermittent regimen has been conducted in Study C34008 and showed potential of more tolerability and safety compared to daily administration in combination regimen. This study is monotherapy, however, intermittent regimen is worthwhile to explore in this study to elucidate monotherapy dose optimization.

The starting dose in this study will be 60 mg QD, which is the same as that in Study C34001, and which is 2 dose levels (40%) lower than the MTD determined in the Western patient population. If 60 mg QD is proven to be safe and tolerable, dose escalation will be conducted in 20 mg increments of daily dose. Based on emerging safety, tolerability, PK data, a lower dose (eg, 40 mg QD) or alternative dosing regimens (eg, 7 days on followed by 7 days off) will be permitted.

4.2.2 Rationale for PK Assessments

In the dose escalation part, intensive PK samples will be collected from all patients during Cycle 1 to permit detailed characterization of TAK-659 plasma and urine PK across different dose levels in East Asian patients with NHL (refer to Section 9.4.17.1 and Appendix A, Table A and Table B). Plasma PK data will be used to characterize single- and repeat-dose concentration-time profiles of

TAK-659, calculate PK parameters, evaluate the dose-exposure relationship, and contribute to population PK analysis. Urine PK data will be used to determine the percentage of the administered TAK-659 dose excreted in urine as unchanged drug, and renal clearance and its minimum contribution to systemic clearance.

In the expansion part, blood samples for plasma PK will be collected via a limited (sparse) sampling schedule to contribute to population PK and exposure-response analyses (refer to Section 9.4.17.2 and Appendix A, Table C and Table D).

Plasma PK data collected in the dose escalation and expansion parts 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. Plasma PK data also may be evaluated in relation to pharmacodynamic effects (changes in serum cytokines/chemokines/serum proteins), as permitted by the data.

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objectives are:

- To determine the safety, tolerability, and MTD and/or RP2D of TAK-659 administered orally QD to East Asian patients with NHL who do not have an effective standard treatment available.
- To characterize the plasma and urine PK of TAK-659 in East Asian patients with NHL.

5.1.2 Secondary Objective

The secondary objective is to evaluate preliminary efficacy of TAK-659 in patients with relapsed and/or refractory NHL.

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5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are:

- Percentage of patients with treatment-emergent AEs (TEAEs).
- Percentage of patients with Grade 3 or higher TEAEs.
- Percentage of patients with serious TEAEs.
- Percentage of patients with DLTs during Cycle 1 (dose escalation part only).
- Percentage of patients discontinuing study drug because of TEAEs.
- Percentage of patients with clinically significant abnormal laboratory values.

- Percentage of patients with clinically significant abnormal vital sign measurements.
- TAK-659 C_{max} on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 T_{max} on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 AUC_{τ} on Cycle 1 Days 1 and 7 or 15 by dose.
- Renal clearance (CL_R) on Cycle 1 Day 7 or 15 by dose.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- Overall response rate (ORR) in the expansion part.
- CR rate in the expansion part.
- Duration of response (DOR) in the expansion part.
- Progression-free survival (PFS) in the expansion part.

The investigators will perform response assessment using modified International Working Group (IWG) 2007 criteria for malignant lymphoma [25], which will be the main analysis for the efficacy endpoints.

5.2.3 Additional Endpoints

Additional endpoints are:

- Apparent oral clearance (CL/F), CL_R as a percentage of CL/F, peak-trough ratio (PTR), accumulation ratio (Rac), and observed concentration at the end of the dosing interval (C_{trough}) on Cycle 1 Day 7 or 15 by dose.
- Plasma concentration-time data contributing to population PK and exposure-response analyses.

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This is an open-label, multicenter, phase 1 study of TAK-659 including a dose escalation part in adult East Asian patients with NHL and an expansion part in adult East Asian patients with relapsed and/or refractory NHL.

The dose escalation part of the study will enroll approximately 18 to 32 East Asian patients diagnosed with NHL for which no effective standard treatment is available. Assuming a dropout rate of 20%, this will ensure that 16 to 28 DLT-evaluable patients are enrolled in the dose escalation part. TAK-659 will be administered continuously, QD, in 28-day treatment cycles (Dosing Schedule A). Dose escalation will follow a standard 3+3 schema to determine the MTD and/or the RP2D. The initial TAK-659 dose will be 60 mg QD and will escalate to 80 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses or regimens, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-659.

If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion between the investigator and the sponsor. If ≥2 of 6 patients experience a DLT at 80 mg QD, alternate dose regimens between 60 and 80 mg (ie, 80 mg 7 days on 7 days off [Dosing Schedule B]) will be evaluated as described below. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the totality of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Intrapatient dose escalation is not allowed in this protocol.

An additional dosing schedule will be tested after implementation of Amendment 02:

- Dosing Schedule B: TAK-659 will be administered QD for 7 consecutive days followed by another 7 days of rest and repeated again (ie, 7 days "on" and 7 days "off"), for a cycle duration of 28 days. The starting dose of 80 mg QD was the maximum administered dose in Dosing Schedule A (2 out of 4 patients presented a DLT in the continuous dosing regimen). However, the alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data. Dose escalation will be governed using the same standard 3+3 schema as described in Section 8.3.

The expansion part of this study will begin once the RP2D has been determined. The expansion part will proceed with dosing of TAK-659 at the RP2D in 28-day cycles. The patient population will consist of East Asian patients with FL or MZL who are relapsed and/or refractory after at least

2 prior lines of chemotherapy and who must be ineligible for or refusal to hematopoietic stem cell transplant. It is expected that approximately 12 response-evaluable patients will be enrolled. Assuming a 20% dropout rate, a total of approximately 15 patients will be enrolled. The objectives of the expansion part are to evaluate the longer-term safety and tolerability of TAK-659 administered at the RP2D, to characterize the PK of TAK-659, and to evaluate the preliminary efficacy of TAK-659 in relapsed and/or refractory FL/MZL as measured by ORR and other efficacy variables, including CR rate, DOR, TTP, and PFS.

At least 1 Japanese patient will be enrolled in each cohort in the dose escalation part. The total number of Japanese patients dosed at the RP2D (either the MTD or a lower dose as determined) will be at least 6 including the dose escalation and expansion parts to ensure adequate characterization of PK and safety in Japanese patients.

On the basis of the geographic distribution of patients enrolled and emerging PK and safety data, additional patients may be added, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region. On the basis of emerging efficacy data, additional groups or patients with FL/MZL may be added to further explore efficacy.

Patients will discontinue treatment if they experience an unacceptable TAK-659-related toxicity. Patients may discontinue therapy at any time. Patients will attend the End of Treatment (EOT) visit 28 days (+10 days) after receiving their last dose of TAK-659 or before the start of subsequent antineoplastic therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs. AEs will be assessed, and laboratory values, vital signs, ophthalmic exams, 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 4.03, effective date 14 June 2010 [26]. DLTs are defined in Section 8.2.

Intensive PK samples (serial blood samples and 2 urine samples) will be collected during Cycle 1 in all patients in the dose escalation part to permit detailed characterization of TAK-659 plasma PK and urine PK across different dose levels. Sparse PK samples will be collected in expansion patients to contribute to population PK and exposure-response analyses. If fewer than 6 Japanese patients are dosed at the RP2D in the dose escalation part, then additional intensive PK samples will be collected during Cycle 1 in a subset of Japanese patients in the expansion part. In total, intensive PK sampling will be performed in at least 6 Japanese patients dosed at the RP2D (either the MTD or a lower dose) among the dose escalation and expansion parts combined to ensure adequate characterization of plasma and urine PK in Japanese patients. Details of the PK measurements are described in Section 9.4.17.

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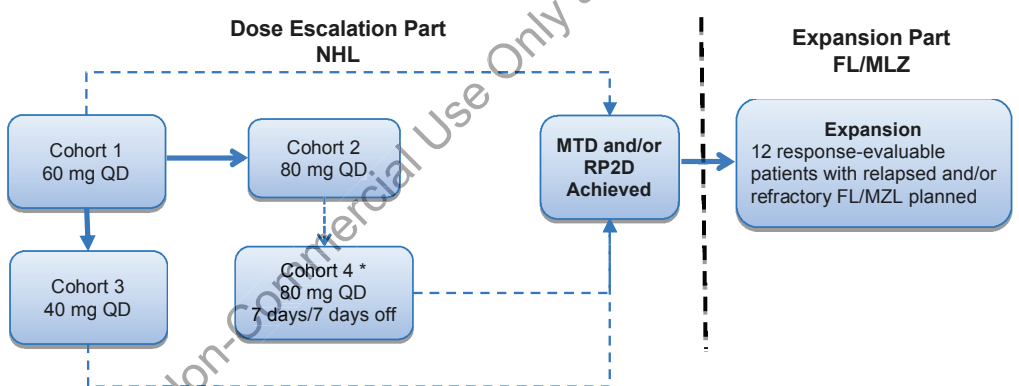
Evaluation of disease response will be performed as described in Section 9.4.15 and the Schedule of Events (Appendix A), using the IWG 2007 modified response criteria for malignant lymphoma (Appendix D) [25]based on investigator assessment. An imaging modality (eg, computed tomography [CT] with contrast and fluoro-2-deoxy-D-glucose [FDG]-positron emission tomography [PET] if appropriate) will be used to follow sites of measurable disease during the study treatment. Radiographic images will be maintained at the site. Based on efficacy data observed, the sponsor can elect to have central collection of disease assessment images. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

The study design is detailed in Figure 6.a.

Figure 6.a Overview of Study Design



FL=follicular lymphoma MTD=maximum tolerated dose, MZL=marginal zone lymphoma, NHL=non-Hodgkin lymphoma, QD=once daily, RP2D=recommended phase 2 dose.
*The alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable.

6.2 Number of Patients

It is expected that approximately 33 to 47 patients will be enrolled in this study from approximately 6 to 10 study sites in East Asia. Enrollment is defined as the time of administration of the first dose of study drug.

For the dose escalation part, approximately 16 to 28 DLT-evaluable patients will be enrolled; assuming a 20% dropout rate, approximately 18 to 32 patients will be enrolled. For the expansion part, approximately 12 response-evaluable patients will be enrolled; assuming a 20% dropout rate, approximately 15 patients will be enrolled.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve a CR, may receive study drug until they experience PD. Patients will discontinue treatment if they have an unacceptable TAK-659-related toxicity.

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

For patients enrolled in the dose escalation part, the maximum duration of treatment will be 12 months unless in the opinion of the investigator and with the agreement with sponsor the patient would derive benefit from continued therapy beyond 12 months.

Patients enrolled in the expansion part who stop treatment for any reason other than PD will continue PFS follow-up every 2 months after the last dose of study drug for up to 6 months or until PD, whichever occurs first.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The primary analysis for safety, PK, and efficacy endpoints and authoring of a CSR may be conducted after all patients enrolled in the study have had the opportunity to complete 4-6 cycles of treatment with study drug and patients who discontinued study treatment must complete safety follow-up. The estimated time frame for primary completion is approximately 47 months. For patients enrolled in the expansion part, PFS follow-up will occur every 2 months after the last dose of study drug for up to 6 months or until PD, whichever occurs first (for patients who discontinue for reasons other than PD). The estimated time frame for study completion is approximately 52 months.

A CSR addendum will be provided to describe additional data not included in the original CSR.

6.3.3 Timeframes 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:		
• Percentage of patients with TEAEs (b).	Percentage of patients with TEAEs.	Through study completion, ~52 months.
• Percentage of patients with Grade 3 or higher TEAEs.	Percentage of patients with Grade 3 or higher TEAEs.	Through study completion, ~52 months.
• Percentage of patients with serious TEAEs.	Percentage of patients with serious TEAEs.	Through study completion, ~52 months.
• Percentage of patients with DLTs during Cycle 1 (dose escalation part only).	Percentage of patients with DLTs during Cycle 1 (dose escalation part only).	4 weeks after last dose of last patient in dose escalation or up to 6 months, if needed
• Percentage of patients discontinuing study drug because of TEAEs.	Percentage of patients discontinuing study drug because of TEAEs.	Through study completion, ~52 months.
• Percentage of patients with clinically significant laboratory values.	Percentage of patients with clinically significant laboratory values, as assessed by the investigator or identified subinvestigator(s).	Through study completion, ~52 months.
• Percentage of patients with clinically significant vital sign measurements.	Percentage of patients with clinically significant vital sign measurements as assessed by the investigator or identified subinvestigator(s).	Through study completion, ~52 months.
• TAK-659 C_{max} on Cycle 1 Days 1 and 7 or 15 by dose.	Geometric mean and CV for C_{max} on Cycle 1 Days 1 and 7 or 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 16.
• TAK-659 T_{max} on Cycle 1 Days 1 and 7 or 15 by dose.	Median (range) for T_{max} on Cycle 1 Days 1 and 7 or 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 16.
• TAK-659 AUC_{τ} on Cycle 1 Days 1 and 7 or 15 by dose.	Geometric mean and CV for AUC_{τ} on Cycle 1 Days 1 and 7 or 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 16.
• CL_R on Cycle 1 Day 7 or 15 by dose.	Geometric mean and CV for CL_R on Cycle 1 Day 7 or 15 by dose in the PK-evaluable population.	Up to Cycle 1 Day 16.

Footnotes are on last table page.

Table 6.a Primary and Secondary Endpoints for Disclosures (continued)

Endpoint	Definition	Maximum Time Frame (a)
Secondary:		
• ORR in the expansion part as assessed by investigators according to modified IWG criteria for malignant lymphoma.	The proportion of patients in the response-evaluable population of the expansion part who achieved either CR or PR, as assessed by investigators, according to modified IWG criteria for malignant lymphoma.	Through study completion, ~52 months.
• CR rate per investigator in the expansion part.	The proportion of patients in the response-evaluable population of the expansion part who achieved CR, as assessed by investigator, according to modified IWG criteria for malignant lymphoma.	Through study completion, ~52 months.
• DOR per investigator in the expansion part.	The time from first documentation of response (CR/PR) to the date of first documentation of PD/relapse, as assessed by investigator, according to modified IWG criteria for malignant lymphoma in the response-evaluable population of the expansion part.	Through study completion, ~52 months.
• PFS per investigator in the expansion part.	The time from the date of first study drug administration to the day of first documented PD or death due to any cause, whichever occurs first, in the safety population of the expansion part, as assessed by the investigator, according to modified IWG criteria for malignant lymphoma.	Through study completion, ~52 months.

AUC_{τ}=area under the plasma concentration-time curve during the dosing interval, CL_R=renal clearance, C_{max}=maximum observed concentration, CR=complete response, CV=coefficient of variation, DLT=dose-limiting toxicity, DOR=duration of response, IWG=International Working Group, ORR=overall response rate, PD=progressive disease, PFS=progression-free survival, PR=partial response, TEAE=treatment-emergent adverse event, T_{max}=time of first occurrence of C_{max}, TTP=time to progression.
(a) Time to last assessment for that endpoint for an individual patient.
(b) 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.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 52 months, including approximately 27 months for the dose escalation part and approximately 25 months for the expansion part including 6 cycles treatment and 6 months PFS follow-up.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

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

1. Male or female patients of East Asian ethnicity (eg, Japanese, Korean, or Chinese) aged 18 years or older (if local regulation requires a minimum age for informed consent of more than 18 years, then patients must be the minimum age or older per the local regulation) when written study informed consent is obtained.
2. To be enrolled to the dose escalation part, patients must have:
   a) Histologically or cytologically confirmed diagnosis of NHL for which no effective standard treatment is available. However, patients with CLL/small lymphocytic lymphoma (SLL), primary CNS lymphoma, or Waldenström macroglobulinemia will be excluded.
   b) Radiographically or clinically measurable disease with at least 1 target lesion. Radiographically measurable disease is determined by IWG 2007 criteria for malignant lymphoma.
3. To be enrolled in the expansion part, patients must meet the following criteria:
   a) Patients must have pathologically confirmed FL (Grade 1, 2, or 3A) or MZL.
   b) Relapsed and/or refractory to ≥2 prior lines of chemotherapy based on standard of care that include at least 1 anti-CD20-based regimen, as well as alkylating agents (eg, cyclophosphamide or bendamustine).
   c) Patients must be ineligible for or refusal to hematopoietic stem cell transplant.
   d) 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.
   e) Must have measurable disease that meets the size criteria per IWG (>1.5 cm in the longest diameter for a lymph node or a nodal mass, or >1.0 cm in the longest diameter for an extranodal disease) as assessed on cross-sectional imaging by CT scan/magnetic resonance imaging (MRI). (CT scan is to be performed with contrast unless it is medically contraindicated.)
4. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (See Appendix E for a description of the ECOG performance status scale).
5. Life expectancy longer than 3 months.
6. Patients must have adequate organ function, including the following:

a) Bone marrow reserve: absolute neutrophil count (ANC) ≥1,000/mm^3, platelet count ≥75,000/mm^3 (≥50,000/mm^3 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 function: total bilirubin ≤1.5×the upper limit of normal range (ULN); alanine aminotransferase (ALT) and AST ≤2.5×ULN.

c) Renal function: creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault equation (refer to Appendix F).

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 and glycosylated hemoglobin [HbA1C] ≤6.5%)

7. Female patients who:

a) Are postmenopausal (natural amenorrhea, not due to other medical reasons) for at least 1 year before the screening visit, OR

b) Are surgically sterile, OR

c) If they are of childbearing potential, 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

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

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

a) Agree to practice effective barrier contraception during the entire study treatment period and 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

8. 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.

9. Recovered (ie, ≤Grade 1 toxicity) from the reversible effects of prior anticancer therapy. Patients with ongoing toxicities at baseline may be eligible; however, any Grade 2 baseline toxicity (except for alopecia) should be discussed with the medical monitor.

7.2 Exclusion Criteria

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

1. 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 (eg, Grade 2 or greater hypertension or lymphopenia, Grade 2 or higher amylase and/or lipase elevations).
4. Life-threatening illness unrelated to cancer that could, in the investigator's opinion, make the patient not appropriate for this study.
5. 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.
   (Note: Female patients who are in the lactation period, even if they discontinue breastfeeding, will be excluded from the study.)
6. 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 agent; ≤8 weeks for cell-based therapy or anti-tumor vaccine).
7. Radiotherapy less than 3 weeks before the first dose of study treatment. If prior radiotherapy occurred <4 to 6 weeks before the study start, as radiated lesions cannot be reliably assessed by FDG-PET, nonradiated target lesions are required for eligibility.
8. Known HIV positive (testing not required).
9. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
   Note: Hepatitis testing will be performed as specified in the Schedule of Events (Appendix A). Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.
10. 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 at any time.

11. Any clinically significant comorbidities, such as uncontrolled pulmonary disease (eg, severe chronic obstructive pulmonary disease with hypoxemia, interstitial lung disease, radiation induced lung injury), known impaired cardiac function or clinically significant cardiac disease (specified below), active CNS disease, or any other condition that could, in the opinion of the investigator, compromise the patient's safety and participation in the study per protocol.
12. Patients with any of the following cardiovascular conditions are excluded:
    - Acute myocardial infarction within 6 months before starting study drug.
    - Current or history of New York Heart Association Class III or IV heart failure (Appendix H).
    - Evidence of current, uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
    - QT interval with Fridericia correction method (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the Screening period.
    - Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that are considered to be clinically significant by the investigator.
13. Major surgery within 14 days before the first dose of study drug or incomplete recovery from any complications from surgery.
14. 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 8.7.1).
15. Treatment with high-dose corticosteroids for anticancer purposes within 7 days before the first dose of TAK-659. Use of corticosteroids at daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.
16. Patient 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.
17. 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.
18. Lack of suitable venous access for the study-required blood sampling for TAK-659.
19. Use or consumption of any of the following substances:
    - 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, the use of these agents is not permitted during the study except for AE management (see Section 8.5 for details). See Appendix I for a nonexhaustive list of strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the US Food and Drug Administration (FDA) Draft DDI Guidance.

- 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, the use of these agents is not permitted during the study except for AE management (see Section 8.5 for details). See Appendix I for a nonexhaustive list of strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the US FDA Draft DDI Guidance.
- 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).

If required by local regulations or local clinical guidelines or preferred by the investigator, study drugs and protocol assessments may be administered in an in-patient setting during Cycle 1.

The study drug will be administered according to the assigned dosing schedule (ie, Dosing Schedule A or B). For Dosing Schedule A, the study drug will be administered continuously, QD, in 28-day cycles. For Dosing Schedule B, the study drug will be administered QD for 7 consecutive days followed by 7 days of rest and repeated again for a 28-day cycle (ie, 7 days "on" and 7 days "off"). 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 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 included in the Pharmacy Manual.

Patients should be instructed to take their study medication at approximately the same time each day and to not take more than the prescribed dose at any time. On visit days, patients should be instructed to hold their dose until predose assessments have been performed. If a patient does not take the TAK-659 dose at the scheduled dosing time (±6 hours), 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 the following day). Patients should record any skipped doses in their dosing diary (see the 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 the Study Manual). Patients should resume dosing at the next scheduled time with the prescribed dosage.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010 [26]. These criteria are provided in the Study Manual. DLT is defined as any of the following events occurring during Cycle 1 that are considered by the investigator to be at least possibly related to therapy with TAK-659.

- Grade 4 neutropenia (ANC <500 cells/mm^3) unresolved to ≤Grade 1 (ANC ≥1500 cells/mm^3) or baseline for more than 7 consecutive days in the absence of growth factor support.

- ≥Grade 3 neutropenia (ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour.
- Grade 4 thrombocytopenia (PLT <25,000/mm^3) unresolved to ≤Grade 1 (PLT ≥75,000/mm^3) or baseline for more than 7 consecutive days, or PLT <10,000/mm^3 at any time.
- ≥Grade 3 thrombocytopenia (<50,000/mm^3) with clinically significant bleeding.
- Any Grade 3 or greater nonhematologic toxicity with the following exceptions:
  - ≥Grade 3 nausea and/or emesis that resolves to <Grade 3 within 3 days after the use of optimal antiemetic treatment based on standard practice. (An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin receptor [5-HT$_3$] antagonist and a corticosteroid given in standard doses and according to standard schedules.)
  - ≥Grade 3 diarrhea that resolves to <Grade 3 within 3 days after receiving the maximal supportive therapy based on standard practice.
  - Grade 3 fatigue that lasts ≤72 hours.
  - Isolated asymptomatic ≥Grade 3 laboratory abnormalities that resolve to ≤Grade 1 or baseline in ≤7 days.
- Receiving <75% of planned doses of study drug (receiving <21 days for Dosing Schedule A and <11 days for Dosing Schedule B) within Cycle 1 because of prolonged treatment interruption caused by TAK-659-related toxicities.
- Other TAK-659-related Grade 2 or greater nonhematologic toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of TAK-659 therapy.

Although DLT-like toxicities may occur at any time during treatment, only DLTs occurring during Cycle 1 of treatment will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored throughout all cycles of therapy for treatment-related toxicities.

8.3 Dose Escalation Rules

Dose escalation will follow a standard 3+3 schema to determine the MTD and/or the RP2D in East Asian patients with NHL. The dose escalation plan, as specified in Table 8.a, is based on the starting dose of 60 mg, the dose determined to be tolerable in the FIH Study C34001 in the Western population. The dose will escalate to 80 mg QD provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses or regimens, and expansion of an existing dose level are all permissible following written confirmation of discussions between the

sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-659.

If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion between the investigator and the sponsor. If ≥2 of 6 patients experience a DLT at 80 mg QD, alternate dose regimens between 60 and 80 mg (ie, 80 mg 7 days on 7 days off) will be evaluated.

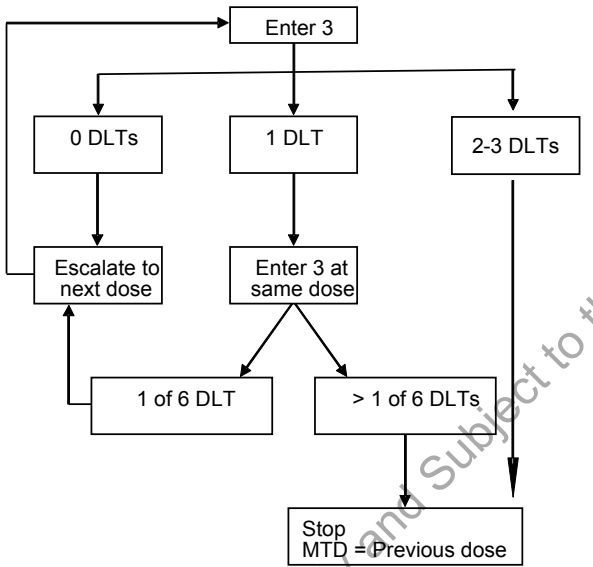
While the primary escalation schema is designed to determine a classic Cycle 1-based MTD, dose escalation may be halted at any time after consultation between the sponsor and investigators if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable RP2D. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Intrapatient dose escalation is not allowed in this protocol.

Escalation rules based on DLTs include:

1. If 0 of 3 patients experience DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.
3. Escalation will continue if 1 of 6 patients experiences DLT.
4. If 2 or more patients in any dose level experience DLT, enrollment at that dose level will stop. Following consultation between the sponsor and investigators, either the previous dose level will be considered the MTD (if 6 or more patients have been studied at that dose level), the previous dose level will be expanded (if fewer than 6 patients have been studied at that dose level), or a dose level intermediate between the current and the previous dose level will be evaluated.

Figure 8.a is a diagrammatic representation of these rules.

Figure 8.a Dose Escalation Algorithm



DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

Table 8.a Planned Dose Levels

Dose Level	Dose (unit)
1	60 mg QD
2	80 mg QD
3	40 mg QD
4	80 mg QD*, 7 days on/7 days off

*The alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data.
More conservative dose escalation, evaluation of intermediate doses or alternative regimens, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-659.

DLT-evaluable patients in each dose cohort will consist of patients who have met the minimum treatment and safety evaluation requirements of the study or who have experienced a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days for Dosing Schedule A and for ≥11 days for Dosing Schedule B (receiving at least 75% of planned doses of TAK-659 in Cycle 1) and observed for ≥28 days following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur. Patients who do not meet these minimum requirements will be regarded as ineligible for inclusion as DLT-evaluable patients for the given dose cohort and may be replaced within the same cohort. However, all AEs

observed in each dose level, including those observed in DLT non-evaluable subjects, will be evaluated in concert with DLTs when making dose escalation decisions during the study.

8.4 Dose Modification Guidelines

8.4.1 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 Cycle 2, 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 4.03. 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 permanently discontinue from the study. Detailed dose modification guidelines are provided in Sections 8.4.4 and 8.4.5. Patients who have a TAK-659 dose held because of a treatment-related or possibly related AE may resume study drug after resolution of the AE, and may either maintain the same dose level or have TAK-659 reduced by at least 1 dose level (dose reduction). Dose reduction levels for TAK-659 are presented in Table 8.b. When a dose reduction occurs, the TAK-659 dose will be reduced to the next lower dose. If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 can be further reduced if the treating physician believes that the patient is benefiting from study treatment and may benefit at a further-reduced dose of TAK-659. When a dose reduction of TAK-659 is required because of toxicity, no dose re-escalation will be permitted. 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 more than 2 dose reductions (more than 1 dose reduction for 40 mg QD) are required in a patient, the patient should be discontinued from study treatment, unless the treating physician believes that the patient may benefit from continued study treatment after resolution of AEs to ≤Grade 1 or baseline. In this case, consultation with the medical monitor or designee is required. Study drug interruption before resolution of AEs to ≤Grade 1 or baseline 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 antineoplastic therapy, whichever occurs first.

Table 8.b Dose Reduction Levels for TAK-659

Dose Reduction Levels	Dose (unit)
Planned dose	40, 60, or 80 mg
(-) 1 dose level	Planned dose minus 20 mg (a)
(-) 2 dose level	Planned dose minus 40 mg (a) (b)

(a) Intermittent regimen (eg, 7 days on/7 days off) may be allowed.
(b) Not applicable to 40 mg QD cohort.

For AEs that occur during the study but are not related to TAK-659, the dose modification of TAK-659, 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 hold the TAK-659 dose until 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).

Patients who experience a DLT (during escalation part) or DLT-like toxicity (expansion part) during the first cycle will, in general, require treatment with TAK-659 to be permanently discontinued. The patient will be followed until resolution or stabilization of the event. 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, then the dose of TAK-659 will be reduced by at least 1 dose level (for example, reduced to a lower dose that has been evaluated and found to be safe and tolerable during dose escalation) when treatment resumes after recovery from the toxicity or toxicities in question to ≤Grade 1 or baseline or to a level considered acceptable by the investigator. This discussion will be documented in the study file. However, if a patient requires a dose delay of >21 days for such an event to resolve despite the best supportive care permissible per the protocol, then the patient must be discontinued from the study.

For management of toxicities on study, dose modification guidelines should be closely followed. However, on the basis of evolving safety data for TAK-659 and 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. Discussions and agreements will be documented.

8.4.2 Intrapatient Dose Escalation

Intrapatient dose escalation is not allowed in this protocol.

8.4.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

TAK-659 is administered in continuous cycles; therefore study drug should be administered continuously or according to the intermittent dosing regimen, unless AEs occur that meet the dose modification criteria outlined below.

Before starting a new treatment cycle, TAK-659-related AEs or laboratory abnormalities must have returned to ≤Grade 1 or baseline levels.

8.4.4 TAK-659 Dose Modification for Hematologic Toxicities

Please refer to Table 8.c for dose delay and reduction recommendations for hematologic toxicities. When the TAK-659 dose is withheld according to the following criteria (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. Upon recovery, TAK-659 may be reinitiated either at the same dose level or at a reduced dose level. For 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 guideline is permissible upon discussion with the sponsor. When a dose reduction of TAK-659 is required, no re-escalation of dose will be permitted.

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

Criteria	Action
Neutropenia (ANC)	
Grade 1 (ANC <LLN-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, 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, then dose reduced by 1 dose level.
Febrile neutropenia (ANC <1000 cells/mm^3, a single temperature of >38.3°C [101°F], or a sustained temperature of ≥38°C [100.4°F] for more than 1 hour)	Withhold dose until resolved to ≤Grade 1 (ANC ≥1500 cells/mm^3) or baseline and fever/infection have recovered, then reduce by 1 dose level.
Thrombocytopenia (PLT)	
Grade 1 (PLT <LLN-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, 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, then reduce by 1 dose level
Grade 3 anemia	Withhold dose until resolved to ≤Grade 1 or baseline, 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 anemia	Withhold dose until resolved to ≤Grade 1 or baseline, then reduce by 1 dose level if patient is not discontinued.

ANC=absolute neutrophil count, LLN=lower limit of normal, PLT=platelets.

8.4.5 TAK-659 Dose Modification for Nonhematologic Toxicities

Please refer to Table 8.d for dose holding and dose reduction recommendations for nonhematologic toxicities. When the TAK-659 dose is withheld according to the criteria in Table 8.d, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently

until the toxicity resolves to ≤Grade 1 or baseline. Upon recovery, TAK-659 dosing may be re-initiated either at the same dose level or at a reduced dose level. For 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 guideline is permissible upon discussion with the sponsor.

Grade 4 nonhematologic toxicities, with the exception of asymptomatic laboratory changes that are considered clinically manageable, 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, 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 baseline. 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 creatine phosphokinase [CPK]), TAK-659 should be held until resolution to ≤Grade 1 or baseline. When the 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.

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

Criteria	Action
All Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 48 hours with optimal antiemetics and antidiarrheals 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 significant 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 within 72 hours with phosphate repletion. • Other Grade 3 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigators.	Hold TAK-659 until resolution to ≤Grade 1 or baseline. • 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 listed, maintain the dose level (no dose hold required). Permanent discontinuation should be considered if the toxicities persist as ≥Grade 3 for more than 21 days despite temporary disruption of study drug.
Grade 4 nonhematologic toxicities with the exception of asymptomatic laboratory change that is considered clinically manageable: • 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 within 72 hours with phosphate repletion. • Other Grade 4 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigators.	Consider permanently discontinuing TAK-659, 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 by ≥1 dose level is required if study treatment resumes after resolution to ≤Grade 1 or baseline. For the exceptions, hold TAK-659 until resolution to ≤Grade 1 or baseline. • If resolved in ≤7 days, maintain dose level. • If resolved in >7 days, reduce dose by 1 dose level. • If recurrence occurs, reduce dose by 1 dose level.

ALT=alanine aminotransferase, AST=aspartate aminotransferase.

8.5 Concomitant Medications and Procedures

During the course of 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 or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant non-drug 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 on 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 disease progression) is not permitted during study. Palliative radiotherapy for local pain/symptom control in a pre-existing non-target lesion, if required, may be considered after discussion with the medical monitor or designee. 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 adverse events.
- 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.
- Primary prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) is not recommended at the study start and in Cycle 1. 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 factors, 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 DDI Guidance.
  - 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.
- Antivirals for HCV: boceprevir, daclatasvir, simeprevir, telaprevir, danoprevir+ritonavir, velpatasvir+sofosbuvir (fixed dose combination), paritaprevir+ritonavir+ombitasvir (fixed dose combination), paritaprevir+ritonavir+ombitasvir+dasabuvir (fixed dose combination).
- Foods/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 due to that AE, the medications listed above and in Appendix I may be used for AE management provided there is no appropriate alternative treatment available based on the investigator's judgment and the dosing is not concurrent with study drug. Treatment with the study drug may then resume after an appropriate washout period for the prohibited concomitant medication (consistent with the washout period as specified in the eligibility criteria for the study). Sites are encouraged to discuss any such situations with the Medical Monitor or designee. Patients should be closely monitored for potential toxicities.

Note that medications used to treat HIV infection are not listed above or in Appendix I because patients with known HIV 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 and in Appendix I, then its use must be discussed with the medical monitor or designee to assess the relative benefit and risk.

8.6 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.

8.6.1 Pregnancy and Contraception

No teratogenicity studies were conducted on animals. 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 the reproductive age group and male patients should use effective methods of contraception throughout defined periods during and after study treatment as specified below:

1) Some examples of effective contraceptive methods include intrauterine devices and hormonal contraceptives.
2) Use only contraceptive methods that are locally approved and available in each country.
3) Female patients must meet 1 of the following criteria:
    - Postmenopausal (natural amenorrhea, not due to other medical reasons) for at least 1 year before the Screening visit, or
    - Surgically sterile, or
    - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing of the informed consent form (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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
4) Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:
    - Agree to 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 true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], condoms only, withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
5) Female patients should not donate ova from the time of signing the informed consent through 180 days after the last dose of study drug.
6) Male patients should not donate sperm from the time of signing the informed consent through 180 days after the last dose of study drug.

8.6.2 Patients With Prior Exposure to HBV or HCV

Patients who have detectable HBV or HCV viral loads are excluded from study participation (see Section 7.2, Exclusion Criterion #8). Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (determined by a negative viral load) are allowed in the study, but should be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV in their blood during the study will have TAK-659 treatment held and will be treated with antivirals medication (eg, nucleoside antagonist [NA] lamivudine for HBV) per local institutional standard practice; a consultation with a hepatologist should be considered.

Restarting TAK-659 after HBV or HCV is no longer detected may be considered in the setting of continued prophylaxis and after a discussion with the sponsor's medical monitor to review the potential benefit versus risk to the patient in the setting of a controlled HBV or HCV infection.

8.7 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed per standard clinical practice, 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 either help establish eligibility for the study or support escalation of study drug dose during the dose escalation part. The said growth factors and blood products cannot be used within 14 days before the first dose of the study; and their use is prohibited during Cycle 1. However, the use of these agents in Cycle 1 is permissible when it is determined to be necessary in the clinical management of the patient following discussions and agreement between the investigator and the sponsor. In such a case, depending on the relatedness of the adverse event to the study drug, the patient will either be replaced for DLT evaluation or the event will be called a DLT.

8.7.1 Prophylaxis Against Infections

8.7.1.1 Cytomegalovirus Monitoring and Prophylaxis

At screening, all patients must have CMV serology and quantitative polymerase chain reaction (PCR) assay performed. CMV monitoring with a quantitative PCR assay will be performed as specified in the Schedule of Events. If positive at baseline, CMV monitoring is advised once a week with a decrease to a monthly frequency as it becomes negative. Preemptive treatment should be initiated based on the local CMV copy number per institutional practice. Prophylactic treatment can be initiated per investigators' discretion based on the risk assessment (even if the CMV test is negative at baseline). Interruption of study drug is generally advised if the positive CMV test is accompanied by associated clinical symptoms or the copy number reaches a level that treatment is indicated per institutional standard or the CMV test remains positive despite the antiviral treatment for CMV. If the study drug is interrupted, it can be resumed only after the infection has resolved. CMV monitoring is advised for the duration of the study as described in Section 9.4.13.3 and in the Schedule of Events (Appendix A).

The following agents could be considered for prophylaxis or pre-emptive treatment against cytomegalovirus: ganciclovir (intravenous [IV]), valganciclovir (PO), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until cytomegalovirus is no longer detected.

8.7.1.2 Prophylaxis for Pneumocystis jirovecii Pneumonia

Patients with lymphopenia may also be prone to developing infections, such as respiratory infections including pneumonia. Consider a diagnosis of opportunistic infection including *Pneumocystis jirovecii* pneumonia (PJP) in patients presenting with shortness of breath, cough, or fever. Prophylaxis for PJP must be initiated (either at baseline or during treatment) if at least 1 of the following is 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 the study treatment. When steroids and/or any immunosuppressive 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 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 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.

8.7.2 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/severe, discontinue TAK-659. Patients should be monitored for respiratory signs and symptoms throughout treatment and should be advised to promptly report respiratory symptoms.

8.7.3 Nausea and/or Vomiting

This study will not initially employ prophylactic antiemetics before the first dose of the study drug during dose escalation. However, patients who develop nausea and/or vomiting will be actively

managed using 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 and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

8.7.4 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 of diarrhea 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.

8.7.5 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 following the dose modification guidelines in Table 8.d.

8.7.6 Rash With or Without Pruritus

Prophylactic measures should also 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.d.

8.7.7 Thrombocytopenia

Blood counts should be monitored regularly as outlined in the Schedule of Events (Appendix A), with additional testing obtained according to standard clinical practice. Administration of TAK-659 should be modified per dose modification guidelines when thrombocytopenia occurs (see Table 8.c). Platelet transfusion is allowed to manage severe thrombocytopenia 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/mm^3 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.

8.7.8 Neutropenia

Blood counts should be monitored regularly as outlined in the Schedule of Events (Appendix A), with additional testing obtained according to standard clinical practice. TAK-659 administration should be modified per dose modification guidelines when neutropenia occurs (see Table 8.c). Myeloid growth factors (eg, G-CSF, GM-CSF) may be used to treat severe and/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 8.5).

8.7.9 Anemia

Hemoglobin should be monitored regularly as outlined in the Schedule of Events (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 or any asymptomatic patients with hemoglobin <8 g/dL to maintain 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 if approved locally and should be administered according to institutional practice.

8.7.10 Hypophosphatemia

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

8.7.11 Enzyme Elevations

8.7.11.1 Transaminase, Amylase and Lipase, and CPK Elevations

Elevations of transaminases, amylase, lipase and CPK have been observed. Events are generally asymptomatic and reversible with dose interruption and not associated with evidence of pathological tissue injuries. See dose modification guidelines in Table 8.d.

8.7.11.2 Lactate dehydrogenase Elevations

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

8.7.12 Fluid Deficit

Fluid deficit should be corrected before initiation of study drug and during treatment.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

TAK-659 has been formulated into immediate-release, film-coated tablets via a common granulation process. Three different tablet dosage strengths, 20 mg, 60 mg, and 100 mg, have been formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets are coated with Opadry film coat.

8.10 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.

8.11 Packaging and Labeling

TAK-659 20 mg, 60 mg, and 100 mg tablets are packaged into round, white, high-density polyethylene bottles with induction seals, desiccant packs, and polypropylene, child-resistant caps. Each bottle of TAK-659 is labeled with either a single-panel or multilanguage label containing pertinent study information, country-specific requirements, and a caution statement.

8.12 Storage, Handling, and Accountability

TAK-659 tablets should be stored in the original dispensing bottles at 1°C to 25°C, with excursions permitted to 30°C as long as they do not exceed 7 days. All temperature excursions for the tablets must be reported back to the sponsor for assessment and determination for continued use. Please refer to the Pharmacy Manual for additional information. TAK-659 tablets must be used before the retest date indicated on the label and/or accompanying documentation. Throughout the clinical trial, the stability of the drug product will be monitored. TAK-659 tablets should remain in the original bottle provided to the investigational site and patients. Drug supplies must be kept in an appropriate, limited access, secure place until they are dispensed to the enrolled patients, returned to sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies received at the clinical sites will be counted and reconciled before being returned to the sponsor.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the subjects, 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. When cleaning up broken tablets, raising dust should be avoided. Damaged tablets may be harmful if inhaled, ingested, or through skin and/or eye contact. If damaged tablets come in contact with the eyes or skin, immediately and thoroughly flush and wash 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 of TAK-659. 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, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the medical monitor for this study, the central laboratory and any additional clinical laboratories and the contract research organization (CRO) team and the interactive voice/web response system may be found in the Study Manual. A full list of investigators is available in the sponsor's or CRO's investigator database.

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 is a phase 1 study that incorporates a dose escalation part and an expansion part at the RP2D (either the MTD or a lower dose as determined). In the dose escalation part, patients will be assigned to a dose cohort using the dose escalation rules as described in Section 8.3. In the expansion part, patients will be assigned as described in Section 6.1.

At least 1 Japanese patient will be enrolled in each cohort in the dose escalation part. The total number of Japanese patients dosed at the RP2D (either the MTD or a lower dose as determined) will be at least 6 including the dose escalation and expansion parts.

9.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, EOT, and PFS follow-up (for patients in the expansion part only). 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 of 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, 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, Table B, Table C and Table D) 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, 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, including a description of prior therapies. In addition, concomitant medications will be recorded as specified in Section 9.4.9. During dose expansion, medical history will also include baseline disease characteristics such as staging, risk/prognostic index, and other individual prognostic evaluations.

9.4.4 Physical Examination

A physical examination will be conducted per standard of care at the times specified in the Schedule of Events (Appendix A). During dose escalation, complete physical examinations will be performed at Screening, on Day 1 of each cycle of treatment, and at EOT. Symptom- or finding-directed physical examinations will be performed on Days 8, 15, and 22 of Cycle 1 and on Day 15 of Cycle 2. During dose expansion, complete physical examinations will be performed at Screening only, and post-Screening physical examinations will be symptom- or finding-directed examinations.

9.4.5 Patient Height and Weight

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

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

9.4.6 Vital Signs

Vital sign measurements include seated position (after the patient has been sitting quietly for approximately 5 minutes in this position) measurements of diastolic and systolic blood pressure, pulse rate, temperature and O_2 saturation will be assessed as specified in the Schedule of Events (Appendix A).

9.4.7 ECOG Performance Status

ECOG performance status will be assessed as specified in the Schedule of Events (Appendix A).

9.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening and again at Cycle 1 Day 1. A urine pregnancy test will be performed predose on Day 1 of all cycles, and negative results must be obtained before the first dose of TAK-659 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.

Women of childbearing potential is defined as any sexually active female patients who meet both of the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy, AND
- Those who have not had natural menopause for 12 consecutive months or longer (eg, follicle-stimulating hormone >40 IU/L and no menopausal period for at least 12 consecutive months; loss of menopausal periods following chemotherapy may not rule out childbearing potential).

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 of the signing of the ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first. See Section 8.5 for information on concomitant medications and procedures.

9.4.10 AEs

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

A 12-lead ECG will be performed and interpreted locally at the time points specified in the Schedule of Events (Appendix A). The ECG schedule is more intensive for patients enrolled in the dose escalation cohorts.

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, pharmacodynamic, or safety laboratory blood sampling 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 ECG to rule out improper lead placement contributing to the ECG abnormality.

Confirmation that the machine-estimates of the rate-corrected QT interval (millisec) of electrocardiograph (QTc) are accurate using the appropriate QT correction formula (QTcF, QT interval with Bazett correction method [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 by a change in medication and/or correction of electrolyte abnormalities, and a repeat ECG meets eligibility requirements, the patient may enroll in 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 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 made by the investigator and the sponsor's clinician on a case-by-case basis.

ECGs 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 locally. Handling and shipment of clinical laboratory samples will be outlined in the Laboratory Manuals.

Clinical laboratory evaluations will be performed as outlined below.

9.4.13.1 Clinical Chemistry, Hematology, and Urinalysis

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	Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Gamma glutamyl transferase (GGT)
Leukocytes with differential	Alanine aminotransferase (ALT)	Glucose
Neutrophils (ANC)	Amylase	Lactate dehydrogenase (LDH) (including LDH isozymes)
Platelets (count)	Aspartate aminotransferase (AST)	Lipase
Lymphocytes (absolute lymphocyte count [ALC])	Bilirubin (total)	Magnesium
Lymphocyte subsets (CD4, CD8, CD4/CD8)	Urea nitrogen	Phosphate
	Calcium	Potassium
	Carbon dioxide (CO_2)	Sodium
	Creatinine	Protein (total protein)
	Creatine kinase (CK)	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 Cockcroft-Gault formula will be employed (refer to Appendix F).

9.4.13.2 Hepatitis Testing

Hepatitis testing will be performed during the Screening period. HBV testing will include HBsAg, HBsAb, and HBcAb. For patients who are HbsAg negative but HBsAb and/or HbcAb positive, HBV DNA will also be assessed at Screening. HCV testing will include HCVAb. Patients who test positive for HCVAb will also be tested for HCV RNA at Screening.

Note that patients who have negative HBsAg but positive HBcAb and/or HBsAb may be enrolled but must have undetectable HBV viral load. Patients who have a positive HCVAb can be enrolled but must have undetectable HCV viral load.

Patients who are HBsAg negative but HBsAb and/or HBcAb positive, and/or HCVAb positive with a negative viral load at Screening, who are enrolled in this study will be monitored by assessment of viral load (DNA titers for HBV, RNA titers for HCV) every 2 months.

9.4.13.3 CMV Testing

Patients will be tested at screening for CMV. CMV will continue to be monitored throughout the study.

Tests at screening include CMV serology (immunoglobulin [Ig]G and IgM) and quantitative PCR for CMV. Quantitative PCR for CMV monitoring will be performed as specified in the Schedule of Events (Appendix A).

9.4.14 Ophthalmic Exam

A slit lamp eye examination will be performed by an ophthalmologist at Screening, Cycle 2 Day 1, Cycle 7 Day 1, 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 Screening but not during the study unless clinically indicated. Additional eye exams may also be performed as required. 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

Response status for all patients will be assessed and reported by the investigators; no independent confirmation of the assessment results is planned.

9.4.15.1 Dose Escalation Part

Patients in the dose escalation part will undergo radiographic evaluation and symptom assessment to monitor and assess disease response. Response assessment will follow the modified IWG 2007 criteria for malignant lymphoma (Appendix D, [25]). CT scans (with contrast) of the neck (if appropriate), chest, abdomen, and pelvis will be performed at Screening (within 28 days before the first study drug administration); at the end of Cycles 2, 4, and 6; at the end of every 3 cycles thereafter (until PD or the start of alternative therapies); and at the EOT visit. An FDG-PET scan extending from the neck through the mid-thighs should be performed only at baseline for tumor types for which it represents standard of care for response assessment. If the screening FDG-PET scan is positive, FDG-PET scans should be repeated either at the time of assessment for CR or for recurrence/progression of disease unless otherwise specified per local standard of care for a given lymphoma subtype. If the screening FDG-PET scan is negative, additional FDG-PET scans need not be performed but could be performed as clinically indicated during the study. PET/CT scans may be used as the source of the CT scan, but the CT component should be performed with IV contrast. The same imaging modality should be used consistently throughout the study to monitor the disease status.

For patients with cutaneous T-cell lymphoma, investigator assessment will be based on a composite assessment of total tumor burden including cutaneous disease, lymph node involvement, and blood (Sezary cells).

The sponsor may request clinical sites to forward for review any original data that support the response determination made by the sites.

9.4.15.2 Expansion Part

Baseline disease status will be assessed by investigator using the modified IWG 2007 criteria for malignant lymphoma (Appendix D, [25]) at Screening (within 28 days before the first study drug administration). Efficacy will be assessed using the same criteria at the end of every 2 cycles up to Cycle 12, at the end of every 3 cycles thereafter (until PD or start of alternative therapies), and at the EOT visit. Response will also continue to be assessed in PFS follow-up every 2 months for patients who discontinue treatment for reasons other than PD until 6 months after the last dose or occurrence of PD, whichever occurs first.

Response assessments should include radiographic imaging (CT and FDG-PET), evaluation of symptoms, and bone marrow aspirate/biopsy if appropriate. The FDG-PET imaging should be done minimally at Screening and at the end of Cycles 2, 6, and 12 if positive at baseline or clinically indicated.

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

1. 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 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. Rather, it is recommended that the patient 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, the patient may remain on study.
2. 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 required, and if infiltrate of lymphoma is shown, a 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 2 months irrespective of duration on study.

9.4.15.2.1 CT Scans

CT scans of the chest, abdomen, and pelvis (neck should be included, if appropriate) will be performed to assess baseline disease at Screening and to assess disease response per the assessment schedule noted above and in the Schedule of Events (Appendix A). All CT scans should be performed with IV or oral contrast (unless medically 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/oral 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/oral contrast to avoid compromising PET results.

9.4.15.2.2 PET Scans

A PET scan with FDG extending from the neck through the mid-thighs will be performed to assess baseline disease at Screening. If the screening FDG-PET scan is positive, FDG-PET scans should be conducted at the end of Cycles 2, 6, and 12, and repeated either at the time of assessment for CR or for recurrence/progression of disease; if the screening FDG-PET scan is negative, additional FDG-PET scans do not need to be conducted at these time points (ie, Cycles 2, 6, and 12) but could be performed as clinically indicated during the study. Examinations should be consistent across all time points, including amount of tracer, location of injection, arm position, and scan delay. 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.

9.4.15.2.3 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, immunohistochemistry 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.

CCI

[redacted]

9.4.17 PK Measurements

The primary aim of PK sampling in this study is to measure the plasma and urine concentrations of TAK-659. However, plasma and urine 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.

Details on collecting, processing, storing, and shipping PK samples are provided in the Laboratory Manual. On days when predose PK samples are to be collected, patients should be instructed to refrain from taking their TAK-659 dose at home so that predose PK samples are collected before TAK-659 dosing in the clinic. The timing of the predose PK samples 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.

The timing, but not the number, of blood or urine PK samples may be changed in the dose escalation and/or expansion parts of the study if emerging data indicate that an alteration in sampling schedule is needed to optimize the characterization of TAK-659 PK in East Asian patients.

9.4.17.1 PK Measurements for the Dose Escalation Part

In all dose escalation patients, blood samples for determination of the plasma concentrations of TAK-659 will be collected at the times indicated in Appendix A, Table A (Dosing Schedule A) or Table B (Dosing Schedule B).

To determine urine concentrations of TAK-659, a spot urine collection will be obtained predose on Cycle 1 Day 1, and a urine collection will be obtained in the clinic either on Cycle 1 Day 15 (for subjects on Dosing Schedule A) or Cycle 1 Day 7 (for subjects on Dosing Schedule B) at 0 to 8 hours postdose. For the 0-to-8-hours-postdose urine collection, patients should void the bladder immediately before TAK-659 administration. This voided urine will not contribute to the urine PK sample collection but may be used for the scheduled urinalysis (safety assessment) as specified in the Schedule of Events for Dose Escalation Part (Appendix A). Urine voided subsequently during the 0-to-8-hours-postdose time frame will be collected for analysis of TAK-659 concentration. At the end of the 8-hour period, patients will void completely to finish the timed urine collection. The 8-hours-postdose plasma PK sample should be collected immediately before the patient's final urine void.

The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on PK sample collection days (Cycle 1 Days 1, 2, 8, 15, 16, and 22 [Dosing Schedule A] or Cycle 1 Days 1, 2, 7, 8, 15 and 22 [Dosing Schedule B]). 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.

9.4.17.2 PK Measurements for the Expansion Part

For expansion patients (except for a potential subset of Japanese patients), blood samples for determination of TAK-659 plasma concentrations will be collected during Cycles 1 through 4 according to a sparse sampling schedule at the times indicated in Appendix A, Table C (Dosing Schedule A) or Table D (Dosing Schedule B). Specifically, blood samples will be collected on Days 1, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2 through 4 (for subjects on Dosing Schedule A) or Days 1, 7 and 21 of Cycle 1 and on Day 7 of Cycles 2 through 4 (for subjects on Dosing Schedule B). No urine PK samples will be collected in expansion patients designated for sparse PK sampling. If fewer than 6 Japanese patients are dosed at the RP2D in the dose escalation part, additional intensive PK samples will be collected during Cycle 1 in a subset of Japanese patients in the expansion part. For this subset, additional blood samples and 2 urine samples should be collected as specified in Appendix A, Table A and Table B.

For all expansion patients, 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.

CCI

[redacted]

CCI [redacted]

9.4.20 Sample Retention

FFPE tumor tissues, CCI [redacted] will be stored at BioStorage Technologies (Indiana USA) up to 15 years from the end of study (as defined by the finalization of the CSR). All samples will be destroyed by a third-party vendor identified by BioStorage Technologies per company standard operating procedures. FFPE tumor tissues will be stored at ambient temperature and serum and buccal epithelial cell DNA samples will be stored at -70ºC.

If patients decide to withdraw their informed consent, the samples will be discarded according to the local procedure, ie, the procedure relevant to where the sample resides at the time of withdrawal. In this case, the investigator is required to inform the sponsor of the patient's intention to withdraw. Test results will not be shared with patients unless required by a local law. The tests performed with these samples are not intended to make determinations about a patient's health or the likelihood a patient will develop any disease, so no test results will be provided to the investigator or put into patient's medical record.

9.5 Completion of Treatment

Patients will be considered to have completed the study treatment if they discontinue treatment with TAK-659 for any of the reasons outlined in Section 9.7.

9.6 Completion of Study

In the dose escalation part, patients will be considered to have completed the study when they have discontinued treatment with TAK-659 for any of the reasons outlined in Section 9.7.

In the expansion part, patients will be considered to have completed the study if:

- They have discontinued treatment because of PD.

They remain on study treatment free of PD for at least 6 months after their first dose of study treatment.

They discontinue study treatment for any reason other than PD and continue on to the PFS follow-up and either:

  - Experience PD before the end of the 6-month follow-up period, or
  - Reach the end of the follow-up period.

The sponsor terminates the study.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

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

- AE, including patients who experience a DLT (during escalation) or DLT-like toxicity (during expansion) during the first cycle, patients with Grade 4 nonhematologic toxicity, and patients with Grade 4 anemia.
- Protocol deviation.
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Pregnancy.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

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 receive <75% of planned doses of TAK-659 in Cycle 1 for reasons other than related AEs during dose escalation will be replaced. Patients in the expansion part who are not evaluable for response will be replaced.

9.8 Withdrawal of Patients From Study

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

- AE.
- Protocol deviation.
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Initiation of hematopoietic stem cell transplant.
- Pregnancy.
- Study terminated by sponsor.
- Withdrawal by subject.

- 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.

9.9 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 project clinician or designee. However, the timing of PK and pharmacodynamic assessments as specified in the Schedule of Events (Appendix A: Table A, Table B, Table C and Table D) 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.

9.10 Posttreatment Follow-up Assessments (PFS) (Expansion Part Only)

Patients enrolled in the expansion part who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visits should be conducted at the study site every 2 months for up to 6 months after the last dose of study drug or until PD, whichever occurs first.

If a patient has transitioned to either autologous 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 Takeda Global Pharmacovigilance department 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 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject 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 or subject 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 which 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, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of 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 transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [26]. 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 a single, comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (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 pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

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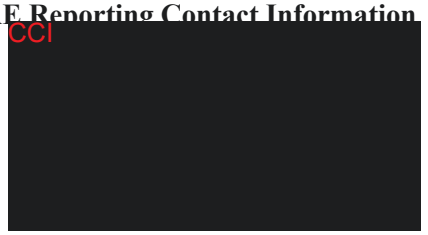

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [26]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (not related) 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 informed consent through 28 days after administration of the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs.
- SAEs
  - Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
  - Related and unrelated, treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 28 days after administration of the last dose of study drug and recorded in the eCRF. 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 e-mail addresses provided below.

Call center	Phone number	E-mail	Fax
DLSS	PPD		

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 CCI [redacted] (refer to Section 10.2).

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

The sponsor or its designee will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs or the head of the study site, 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 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor or its designee 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 also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

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, pretreatment events, 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 subject 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 designee) 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 subject'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 following procedure applies for all countries except Japan. 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 subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs including the audit trail, 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 subject'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.

The following procedure applies for Japan sites only:

The investigator and the head of the institution agree 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 subjects, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), copies of all paper CRFs and query responses/electronic copy of eCRFs including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, and the sponsor (or designees). Any source documentation printed on degradable, thermal-sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 3 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 3 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/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution 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 will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. No formal statistical hypothesis testing will be performed.

13.1.1 Analysis Sets

Analysis sets will include the following:

- Safety analysis set: patients who receive at least 1 dose of study drug. The safety analysis set will be used for all safety analyses and for efficacy analyses.
- PK analysis set: patients who have sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for noncompartmental PK analysis.
- Response-evaluable set: patients who receive at least 1 dose of study drug, have sites of measurable disease at baseline, and have at least 1 postbaseline disease assessment. Analyses of responses will use the response-evaluable set.
- DLT-evaluable set: patients who have met the minimum treatment and safety evaluation requirements of the study or who experience a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if in Cycle 1, the patient is treated with at least 75% of planned doses of TAK-659, is observed for ≥28 days following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by the sponsor and the investigators to conclude that a DLT did not occur.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized, including sex, age, race, weight, height, primary diagnosis, and other parameters as appropriate. No inferential statistics will be done.

13.1.3 Efficacy Analysis

Efficacy is not the primary endpoint of this study. Secondary efficacy endpoints are ORR, CR rate, DOR, TTP, PFS, in expansion patients. ORR is defined as the proportion of patients who achieved CR and PR in the response-evaluable set. CR rate is defined as the proportion of patients who achieved CR in the response-evaluable set. DOR is defined as the time from the date of first documentation of response to the date of first documentation of PD/relapse. TTP is defined as the time from the date of first study drug administration to the date of first documentation of PD by the investigator. PFS is defined as the time from the date of first study drug administration to the day of first documentation of PD or death due to any cause, whichever occurs first. Analyses of ORR, CR, and DOR will use the response-evaluable set. Analyses of TTP and PFS will use the safety analysis set.

Analysis of efficacy measures will be descriptive. Antitumor activity of TAK-659 will be determined by the best overall response. Response will be assessed using IWG criteria for lymphoma at each time point, and the best overall response for each patient will be derived programmatically from among the reported responses. Data listings will present the tumor measurements from CT or FDG-PET (including changes from baseline), disease response category (eg, CR, PR, stable disease [SD]), DOR, and others as appropriate.

The number and percentage of patients falling into each response category (eg, CR, PR, SD) will be tabulated descriptively. Estimates of the CR+PR rate will be presented with 2-sided 95% exact binomial confidence intervals. Response rate will also be tabulated by baseline prognostic factors if applicable. The prognostic factors will include, but will not be limited to, age, number and types of prior therapy, TTP from diagnosis or prior therapy, prior ASCT, and International Prognostic Index score. PFS will be analyzed using the standard Kaplan-Meier method for survival analysis.

For all analyses related to response and PFS, investigator assessments per IWG 2007 will be used for the primary analysis.

13.1.4 PK Analysis

The plasma and urine concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods. For patients who undergo intensive or sparse PK sampling in either dose escalation or expansion, plasma TAK-659 concentrations will be summarized by descriptive statistics according to nominal (scheduled) time postdose, dose level, day and cycle. For patients who undergo intensive PK sampling in either dose escalation or expansion, mean and individual plasma TAK-659 concentration data from Cycle 1will be plotted over time and grouped according to dose level and day, including a graphical presentation of mean and individual concentration-time data in the Japanese patients at the RP2D who undergo intensive PK assessments. All plasma and urine concentration data will be listed by patient, dose level, dosing cycle and day, and nominal and actual time point.

13.1.4.1 Noncompartmental PK Analysis

Plasma and urine PK parameters for patients with intensive PK sampling will be estimated in the PK analysis set using noncompartmental methods. The following PK parameters will be determined as permitted by available data: C_{max}, T_{max}, AUC_{τ}, CL/F, C_{trough}, Rac, PTR, CL_R, and CL_R as a percentage of CL/F. PK parameters will be summarized using descriptive statistics according to dose level and dosing cycle and day, including descriptive summarization of PK parameters in the Japanese patients administered the RP2D who undergo intensive PK assessments to permit noncompartmental PK analysis. Individual PK parameters will be listed by patient, dose level, and dosing cycle and day.

13.1.4.2 PK Sampling Intended to Support Population PK and Exposure-Response Analyses

The plasma PK data collected in the dose escalation and expansion parts of this study are intended to contribute to population PK, exposure-safety, and exposure-efficacy analyses of TAK-659. These analyses may include data collected from other TAK-659 clinical studies. As applicable, the

specifics of the population PK and exposure-response analyses will be described in separate analysis plans, and results will be reported separately from the CSR.

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[redacted]

13.1.7 Safety Analysis

The incidence of DLT will be tabulated for each dose group. In addition, to assess the relationship between toxicities and TAK-659 dose, the preferred terms for individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-evaluable set will be used for the analysis of DLT.

Safety will be evaluated by the frequency of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated. TEAEs that occur after administration of the first dose of study drug and through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.

- Grade 3 or higher TEAEs.
- Grade 3 or higher, drug-related TEAEs.
- Serious TEAEs.
- Drug-related serious TEAEs.
- TEAEs leading to study drug discontinuation.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated to show changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the TAK-659 safety profile.

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

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of TAK-659.

13.1.7.1 ECG Analysis

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

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

No formal statistical power calculations to determine sample size were performed for this study.

It is estimated that 16 to 28 DLT-evaluable subjects will be enrolled in the dose escalation part. The actual number of patients may vary depending on the actual doses being tested. Assuming a 20% dropout rate, 18 to 32 patients will be enrolled in the dose escalation part.

For the expansion part, approximately 12 response-evaluable patients will be enrolled to allow adequate assessment of safety and a preliminary assessment of efficacy. Assuming a 20% dropout rate, approximately 15 patients will be enrolled in the expansion part.

The actual number of patients enrolled may increase on the basis of emerging data to allow a sufficient number of PK/safety-evaluable patients per country or in the East Asian race group or to further assess efficacy in a specific subtype or group of patients with FL or MZL.

The probability of observing at least 4 responders in the 12 response-evaluable patients is 0.775 if the true TAK-659 response rate is 40% (can be considered the true positive rate); the probability of observing at least 4 responses in the 12 response-evaluable patients is 0.205 if the true TAK-659 response rate is 20% (can be considered the false positive rate). See Table 13.a for more details.

Table 13.a Probabilities of Observing the Minimum Number of Responders Given True Response Rates, Assuming a Total of 12 Response-Evaluable Patients

Number of Responders	TAK-659 True Response Rate			
	0.2	**0.4**	**0.6**	**0.8**
≥2	0.725	0.980	1	1
≥3	0.442	0.917	0.997	1
≥4	0.205	0.775	0.985	1
≥5	0.073	0.562	0.943	0.999
≥6	0.019	0.335	0.842	0.996
≥7	0.004	0.158	0.665	0.981

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 (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject 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 subjects. 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 inclusion or exclusion criteria.

The site should document all protocol deviations in the subject'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 subject, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The procedure below applies to Japanese sites only:

The investigator can deviate from and change the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without prior written agreement with the sponsor or a prior approval from the IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible, and approval from the IRB should be obtained.

The investigator should document all protocol deviations.

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 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, subjects) 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 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 requirements of each participating country. 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.

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 investigator's brochure, a copy of the ICF, and, if applicable, subject 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 subject 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. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor or its designee will notify site once the sponsor or its designee has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor or its designee has received permission from the 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 subjects, 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.

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

15.2 Subject Information, Informed Consent, and Subject 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, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as 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 subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject 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, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject'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 subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor or its designee may requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK Medicines and Healthcare products Regulatory Agency, Japan Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject'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 subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed (eg, subject name, address, and other identifier fields not collected on the subject'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 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 on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects 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 subject 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 (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject 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 subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject 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 Dose Escalation Part (Dosing Schedule A and Dosing Schedule B) (28-Day Cycles)

	Screening (a)	Cycle 1							Cycle 2			Cycles 3 and Beyond		EOT (b) (+10 days)
		Day 1	Day 2	Day 7	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 22	Day 1	Day 22	
Dosing														
TAK-659 administration (c)		TAK-659 is dosed orally according to dosing schedule												
Study Procedures														
Informed consent (d)	X													
Inclusion/exclusion criteria	X													
Demographics	X													
Medical history (e)	X	X												
Physical examination (e)	X	X			X	X		X	X	X		X		X
Height	X													
Weight (f)	X	X							X			X		X
Vital signs (g)	X	X			X	X		X	X	X		X		X
ECOG performance status	X	X							X			X		X
12-lead ECG (h)	X	Refer toTable A for Dosing Schedule A and Table B for Dosing Schedule B							X			X		X
Monitoring of concomitant medications and procedures	Recorded from the signing of 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 the signing of ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.													
SAE reporting	**SAEs (i)** will be reported from signing of the ICF through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy.													
Patient diary review (j)		X			X	X		X	X	X		X		X
Imaging/Response Assessments														
Tumor assessment by IWG (CT/FDG-PET) (k)	X										X (k)		X (k)	X

Footnotes are on last table page.

Schedule of Events for Dose Escalation Part (Dosing Schedule A and Dosing Schedule B) (28-Day Cycles) (continued)

	Screening (a)	Cycle 1							Cycle 2			Cycles 3 and Beyond		EOT (b) (+10 days)
		Day 1	Day 2	Day 7	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Day 22	Day 1	Day 22	
Samples/Laboratory Assessments														
Pregnancy test (l)	X	X							X			X		
HBV and HCV screening (m)	X													
CMV testing (n)	X	X							X			X		X
Hematology/chemistry (o) (p)	X	X			X	X		X	X	X		X		X
LDH isozymes (p)		X			X	X			X	X		X (q)		
CK testing (p)	X	X			X	X		X	X	X		X		X
Urinalysis (for hematuria and proteinuria evaluation) (r) (p)	X					X			X			X		X
Ophthalmic exam (s)	X								X			X (s)		X
CCI [redacted]														
Archival (banked) tumor tissue sample (u)	X													
Fresh tumor tissue biopsy if archival banked tumor is not available (v)	X													
Blood samples for PK (w)		Refer to Table A for Dosing Schedule A and Table B for Dosing Schedule B												
Urine samples for PK (x)		Refer to Table A for Dosing Schedule A and Table B for Dosing Schedule B												
CCI [redacted]														

CK=creatine kinase, CMV=cytomegalovirus, CT=computed tomography, CYP=cytochrome P450, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, FDG=fluoro-2-deoxy-D-glucose, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IWG=International Working Group, PBMC=peripheral blood mononuclear cell(s), PCR= polymerase chain reaction, PET=positron emission tomography,

PK=pharmacokinetic(s).

Evaluations/laboratory assessments performed on visit days must take place before dosing unless otherwise indicated. On these days, patients should be instructed to hold dosing until relevant assessments have been completed.

(a) Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. Screening assessments performed no more than 3 days before Cycle 1 Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.

(b) End of treatment will occur 28 days (+10 days) after the last dose of study drug or before the start of subsequent anticancer therapy if that occurs sooner.

(c) TAK-659 will be administered orally once daily in 28-day cycles.

(d) Informed consent may be obtained before the Screening period (within 28 days before Cycle 1 Day 1 dosing).

(e) The Cycle 1 Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1 Day 1). Complete physical examinations will be performed during Screening, on Day 1 of each cycle, and at the EOT visit. Symptom- or finding-directed physical examinations will be performed on Days 8, 15, and 22 of Cycle 1 and on Day 15 of Cycle 2.

(f) Weight should be obtained at Screening, Day 1 predose of each cycle, and at EOT.

(g) Vital signs measurement (blood pressure, pulse rate, temperature, O_2 saturation) should be performed before dosing.

(h) In Cycle 1, single 12-lead ECGs will be performed as detailed in Table A (Dose Escalation Part [Dosing Schedule A] PK, ECG, and Pharmacodynamic Assessment Schedule) or Table B (Dose Escalation Part [Dosing Schedule B] PK, ECG, and Pharmacodynamic Assessment Schedule). For Cycle 2 and beyond, the ECGs will be performed only on Day 1 predose.

(i) All SAEs occurring after consent will be reported to the Takeda Global Pharmacovigilance department or designee (see Section 10.2).

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

(k) Response assessments for lymphoma using the modified IWG 2007 criteria for malignant lymphoma (Appendix D) will be performed at Screening; between Days 22 and 29 (predose) of Cycles 2, 4, and 6; between Days 22 and 29 (predose) of every 3 cycles thereafter; and at the EOT visit. At Screening, chest, abdomen, and pelvis (neck should be included, if appropriate) should be imaged by CT scan with contrast. FDG-PET scans should be performed at baseline only in tumor types for which it represents standard of care for response assessment. If the screening FDG-PET scan is positive, FDG-PET scans should be repeated either at the time of assessment for CR or for recurrence/progression of disease unless otherwise specified per local standard of care. If the screening FDG-PET scan is negative, additional FDG-PET scans need not be performed but could be performed as clinically indicated during the study. See Section 9.4.15.1. If the patient has had an appropriate CT or FDG-PET scan performed within 28 days before Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at Screening. The sponsor may request clinical sites to forward for review any original data that support the response determination made by the sites.

(l) A serum pregnancy test will be performed for women of childbearing potential at Screening and again at Cycle 1 Day 1. A urine pregnancy test must be performed predose on Day 1 of all cycles, with negative results available before the first dose of TAK-659 may be administered in that cycle. If a serum pregnancy test is performed within 3 days before the first dosing and the result is negative, the urine pregnant test may be waived on Cycle 1 Day 1.

(m) Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (determined by a negative viral load) are allowed in the study, but should be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV in their blood during the study will have TAK-659 treatment held and will be treated with antivirals medication (eg, neucleoside antagonist [NA] lamivudine for HBV) per local institutional standard practice; a consultation with a hepatologist should be considered.

(n) CMV serology (IgG and IgM) and quantitative PCR assay will be performed during Screening; quantitative PCR will be performed on Day 1 of each cycle; and

at the EOT visit.
(o) The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated at Cycle 1 Day 1.
(p) Laboratory assessments can be conducted within ±3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise noted.
(q) Cycles 3 and 4 only.
(r) Urinalysis samples will be collected predose and analyzed at the site's local laboratory.
(s) An ophthalmic exam should be performed at Screening, Cycle 2 Day 1, Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 9.4.14 for details.
CCI [redacted]
(u) Archival (banked) tumor tissue samples should be obtained, if available, from the diagnosis specimens or a previous resection or biopsy that was done as part of the patient's standard care. The archival (banked) tumor tissue samples are to be collected only from enrolled patients and may be sent to the sponsor (or designee) after initiation of protocol treatment. Suitable specimens are either a tumor block or a minimum of 10 unstained slides. If archived tumor tissue is not available, an optional fresh tumor biopsy may be obtained. See Section 9.4.16 and the Laboratory Manual for details about sample collections and shipment procedures.
(v) An optional fresh tumor biopsy may be obtained in the absence of archived tumor tissue. See Section 9.4.16 and the Laboratory Manual for details about sample collections and shipment procedures.
(w) Blood specimens for plasma PK analysis will be collected during Cycle 1 in all dose escalation cohorts at time points specified in Table A (Dose Escalation Part [Dosing Schedule A] PK, ECG, and Pharmacodynamic Assessment Schedule) or Table B (Dose Escalation Part [Dosing Schedule B] PK, ECG, and Pharmacodynamic Assessment Schedule).
(x) Urine specimens for urine PK analysis will be collected during Cycle 1 in all dose escalation cohorts at time points specified in Table A (Dose Escalation Part [Dosing Schedule A] PK, ECG, and Pharmacodynamic Assessment Schedule) or Table B (Dose Escalation Part [Dosing Schedule B] PK, ECG, and Pharmacodynamic Assessment Schedule). The PK samples will consist of a Cycle 1 Day 1 predose spot urine collection and a Cycle 1 Day 15 in-clinic 0-to-8-hours-postdose urine collection. Note that 2 urine samples will be collected on Cycle 1 Day 15: a predose specimen for urinalysis (safety assessment) and the 0-to-8-hours-postdose specimen for PK analysis.
CCI [redacted]

Table A Dose Escalation Part (Dosing Schedule A) PK, ECG, and Pharmacodynamic Assessment Schedule

	Cycle 1																	
	Day 1					Day 2 (24 h After Day 1 Dose ±1 h)	Day 8			Day 15					Day 16 (24 h After Day 15 Dose ±1 h)	Day 22		
	Single ECG	PK		PD		PK	PK	PD		Single ECG	PK		PD		PK	PK	PD	
		Plasma	Urine	Serum	PBMC	Plasma	Plasma	Serum	PBMC		Plasma	Urine	Serum	PBMC	Plasma	Plasma	Serum	PBMC
Predose (within 1 hour before dosing on all days) (a)	X (b)	X	X (c)	X	X	X	X	X	X	X (b)	X		X	X	X	X	X	X
0.5 hours postdose (±10 min)		X									X	X (d) (0–8 h [±1 h])						
1 hour postdose (±10 min)		X									X							
2 hours postdose (±20 min)	X	X								X	X		X (e) (2 h or 4 h postdose)			X(f)	X (e) (2 h or 4 h postdose)	
3 hours postdose (±30 min)		X									X							
4 hours postdose (±30 min)		X									X							
8 hours postdose (±30 min)		X									X							

ECG=electrocardiogram, PBMC=peripheral blood mononuclear cell(s), PD=pharmacodynamic, PK=pharmacokinetic.
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 collection of the blood samples.
The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on days of PK sample collection. 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 day of PK sample collection.

(a) 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. The timing of the predose samples on Days 2, 8, 15, 16, and 22 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.
(b) Predose ECG may be performed outside the 1 hour window before dosing.
(c) A predose spot urine specimen will be collected at Cycle 1 Day 1 before first study drug dose administration. See the Laboratory Manual for details on urine collection methodology.
(d) On Day 15, patients will void the bladder immediately before study drug administration. This voided urine will not contribute to the urine PK sample collection but may be used for the scheduled urinalysis (safety assessment) as specified in the Schedule of Events for Dose Escalation Part. Urine voided subsequently during the 0-to-8-hours-postdose time frame will be collected for PK analysis. At the end of the 8-hour period, patients will void completely to finish the timed urine collection. The 8-hours-postdose plasma PK sample should be collected immediately before the patient's final urine void. See the Laboratory Manual for details on urine collection methodology.
(e) On Cycle 1 Day 15 and Cycle 1 Day 22, serum samples for pharmacodynamic assessment of circulating cytokines/chemokines/serum proteins consist of a predose sample and a postdose sample. One postdose sample must be collected when the 2-hour or the 4-hour postdose PK sample is collected.
(f) The postdose PK sample on Cycle 1 Day 22 should be collected between the 2- or 4-hours postdose timeframe (at the same time the 2- or-4 hours postdose sample for pharmacodynamic assessment is collected).

Table B Dose Escalation Part (Dosing Schedule B) PK, ECG, and Pharmacodynamic Assessment Schedule

	Cycle 1																	
	Day 1					Day 2 (24 h After Day 1 Dose ±1 h)	Day 7				Day 8 (24 h After Day 7 Dose ±1 h)		Day 15			Day 22 (24 h After Day 21 Dose ±1 h)		
	Single ECG	PK		PD		PK	Single ECG	PK		PD	PK	PD	PK	PD		PK	PD	
		Plasma	Urine	Serum	PBMC	Plasma		Plasma	Urine	Serum	Plasma	PBMC	Plasma	Serum	PBMC	Plasma	Serum	PBMC
Predose (within 1 hour before dosing on all days) (a)	X (b)	X	X (c)	X	X	X	X (b)	X		X	X	X	X	X	X	X	X	X
0.5 hours postdose (±10 min)		X						X	X (d) (0–8 h [±1 h])	X (e) (2 h or 4 h postdose)								
1 hour postdose (±10 min)		X						X										
2 hours postdose (±20 min)	X	X					X	X										
3 hours postdose (±30 min)		X						X										
4 hours postdose (±30 min)		X						X										
8 hours postdose (±30 min)		X						X										

ECG=electrocardiogram, PBMC= peripheral blood mononuclear cell(s), PD=pharmacodynamic, PK=pharmacokinetic.
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 collection of the blood samples.
The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on days of PK sample collection. 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 day of PK sample collection.

(a) 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. The timing of the predose samples on Days 2, 7, 8, 15 and 22 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.
(b) Predose ECG may be performed outside the 1 hour window before dosing.
(c) A predose spot urine specimen will be collected at Cycle 1 Day 1 before first study drug dose administration. See the Laboratory Manual for details on urine collection methodology.
(d) On Day 7, patients will void the bladder immediately before study drug administration. This voided urine will not contribute to the urine PK sample collection but may be used for the scheduled urinalysis (safety assessment) as specified in the Schedule of Events for Dose Escalation Part. Urine voided subsequently during the 0-to-8-hours-postdose time frame will be collected for PK analysis. At the end of the 8-hour period, patients will void completely to finish the timed urine collection. The 8-hours-postdose plasma PK sample should be collected immediately before the patient's final urine void. See the Laboratory Manual for details on urine collection methodology.
(e) On Cycle 1 Day 7, serum samples for pharmacodynamic assessment consist of a predose sample and a postdose sample. One postdose sample must be collected when the 2-hour or the 4-hour postdose PK sample is collected.

Schedule of Events for Expansion Part (Dosing Schedule A and Dosing Schedule B) (28-Day Cycles)

	Screening (a)	Cycle 1 Days								Cycle 2 Days				Cycles 3 and Beyond Days			EOT (b) (+10 days)	PFS (c)
		1	2	7	8	15	16	21	22	1	7	15	22	1	7	22		
Dosing																		
TAK-659 administration (d)		TAK-659 is dosed orally according to dosing schedule.																
Study Procedures																		
Informed consent (e)	X																	
Inclusion/exclusion criteria	X																	
Demographics	X																	
Medical history (f)	X	X																
Physical examination (f)	X	X			X	X			X	X		X		X			X	X
Height	X																	
Weight (g)	X	X								X				X			X	
Vital signs (h)	X	X			X	X			X	X		X		X			X	X
ECOG performance status	X	X								X				X			X	
12-lead ECG (i)	X	X								X				X			X	
Monitoring of concomitant medications and procedures	Recorded from the signing of 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 the signing of ICF through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.																	
SAE reporting	**SAEs (j)** will be reported from signing of the ICF through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy.																	
Patient diary review (k)		X			X	X			X	X		X		X			X	

Footnotes are on last table page.

Schedule of Events for Expansion Part (Dosing Schedule A and Dosing Schedule B) (28-Day Cycles) (continued)

	Screening (a)	Cycle 1 Days 1	2	7	8	15	16	21	22	Cycle 2 Days 1	7	15	22	Cycles 3 and beyond Days 1	7	22	EOT (b) (+10 days)	PFS (c)
Imaging/Response Assessments																		
Tumor assessment for lymphoma by IWG (CT/FDG-PET) (l)	X												X (l)			X (l)	X	X
Samples/Laboratory Assessments																		
Pregnancy test (m)	X	X							X	X				X				
HBV and HCV screening (n)	X																	
CMV testing (o)	X	X								X				X			X	
Hematology/chemistry (p) (q)	X	X			X	X			X	X		X		X			X	
LDH isozymes (q)		X			X	X				X		X		X (r)				
CK testing (q)	X	X			X	X			X	X		X		X			X	
Urinalysis (for hematuria and proteinuria evaluation) (q) (s)	X									X				X			X	
Ophthalmic exam (t)	X									X				X (t)			X	
CCI [redacted]																		
CCI [redacted]																		
CCI [redacted]																		

Footnotes are on last table page.

Schedule of Events for Expansion Part (Dosing Schedule A and Dosing Schedule B) (28-Day Cycles) (continued)

	Screening (a)	Cycle 1 Days								Cycle 2 Days				Cycles 3 and beyond Days			EOT (b) (+10 days)	PFS (c)
		1	2	7	8	15	16	21	22	1	7	15	22	1	7	22		
CCI [redacted]																		
Blood samples for sparse PK (z)		Refer to Table C for Dosing Schedule A and Table D for Dosing Schedule B																
Blood samples for intensive PK		Samples may be required only in a subset of Japanese patients as specified in Table A and in Table B.																
Urine samples for PK		Samples may be required only in a subset of Japanese patients as specified in Table A and in Table B.																
Bone marrow biopsy and aspirate (aa)	X																	

CK=creatine kinase, CMV=cytomegalovirus, CT=computed tomography, CYP=cytochrome P450, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End of Treatment, FDG=fluoro-2-deoxy-D-glucose, HBV=hepatitis B virus, HCV=hepatitis C virus, ICF=informed consent form, IWG=International Working Group, MRI=magnetic resonance imaging, MTD=maximum tolerated dose, PBMC=peripheral blood mononuclear cell(s), PCR=polymerase chain reaction, PET=positron emission tomography, PFS=progression-free survival, PK=pharmacokinetic(s), RP2D=recommended phase 2 dose.
Evaluations/laboratory assessments performed on visit days need to take place before dosing unless otherwise indicated. On these days, patients should be instructed to hold dosing until relevant assessments have been completed.
(a) Screening assessments are performed within 28 days before the first dose of study drug. Screening assessments performed no more than 3 days before Cycle 1 Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.
(b) End of treatment will occur 28 days (+10 days) after the last dose of study drug or before the start of subsequent anticancer therapy if that occurs sooner.
(c) Patients who stop treatment for any reason other than progressive disease (PD) will continue to have PFS follow-up visits. The PFS follow-up visits should be conducted at the site every 2 months from last dose of study drug up to 6 months or until PD, whichever occurs first.

(d) TAK-659 will be administered orally once daily on 28-day cycles at the RP2D (the MTD or a lower dose as determined).
(e) Informed consent may be captured before the Screening period (within 28 days before Cycle 1 Day 1 dosing).
(f) The Cycle 1 Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1 Day 1). A complete physical examination should be performed at Screening. Postscreening physical examinations will be symptom directed or finding directed.
(g) Weight should be obtained at Screening, predose on Day 1 of each cycle, and at EOT.
(h) Vital signs measurement (blood pressure, pulse rate, temperature, O_2 saturation) should be performed before dosing.
(i) Single 12-lead ECGs will be performed at Screening, predose on Day 1 of each cycle, and at EOT.
(j) SAE reporting will include serious pretreatment events. Only those SAEs that occur after the first dose of study drug will be collected in the eCRF. However, all SAEs occurring after consent will be reported to the Takeda Global Pharmacovigilance department or designee (see Section 10.2).
(k) The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.
(l) Response assessments for follicular lymphoma (FL)/marginal zone lymphoma (MZL) using the modified IWG 2007 criteria for malignant lymphoma, (Appendix D), 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; between Days 22 and 29 (predose) of every 2 cycles up to Cycle 12; between Days 22 and 29 (predose) of every 3 cycles thereafter (until PD, or start of alternative therapies); and at the EOT visit. Response will continue to be assessed in PFS follow-up every 2 months for patients who discontinue treatment for reasons other than PD until 6 months after the last dose or occurrence of PD, whichever occurs first. An FDG-PET scan extending from the neck through the mid-thighs will be performed at Screening for all patients enrolled. If the screening FDG-PET scan is positive, FDG-PET scans should be conducted at the end of Cycles 2, 6 and 12) and repeated either at the time of assessment for complete response (CR) or for recurrence/progression of disease; if the screening FDG-PET scan is negative, additional FDG-PET scans need not be performed at these time points (ie, Cycles 2, 6 and 12) but could be performed as clinically indicated during the study. If the patient has had an appropriate FDG-PET or CT scan performed within 28 days before Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at Screening; see Section 9.4.05.2. Central collection of disease assessment images by sponsor or designee is required.
(m) A serum pregnancy test will be performed for women of childbearing potential at Screening and again at Cycle 1 Day 1. A urine pregnancy test must be performed predose on Day 1 of all cycles, with negative results available before the first dose of TAK-659 may be administered in that cycle. If a serum pregnancy test is performed within 3 days before the first dose and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1.
(n) Patients with prior exposure to HBV or HCV who have subsequently cleared the infection (determined by a negative viral load) are allowed in the study, but should be monitored for reactivation every 2 months. Patients who develop detectable HBV or HCV in their blood during the study will have TAK-659 treatment held and will be treated with antivirals medication (eg, neucleoside antagonist [NA] lamivudine for HBV) per local institutional standard practice; a consultation with a hepatologist should be considered.
(o) CMV serology (IgG and IgM) and quantitative PCR assay will be performed during Screening; quantitative PCR will be performedon Day 1 of each cycle; and at the EOT visit.
(p) The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated at Cycle 1 Day 1.
(q) Laboratory assessments can be conducted within ±3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise noted.
(r) Cycles 3 and 4 only.

(s) Urinalysis samples will be collected predose and analyzed at the site's local laboratory.
(t) An ophthalmic exam should be performed at Screening, Cycle 2 Day 1, Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 9.4.14 for

CCI [redacted]

(x) CCI [redacted]

(y) An optional fresh tumor biopsy may be obtained in the absence of archived tumor tissue. See Section 9.4.16 and the Laboratory Manual for details about sample collections and shipment procedures.
(z) In the expansion patients who undergo sparse PK sampling, blood specimens for plasma PK analysis will be collected at the time points specified in Table C or Table D.
(aa) A bone marrow biopsy and aspirate will be collected at Screening and as necessary for confirmation of CR or at the time of suspected PD per standard practice. A bone marrow aspirate/biopsy could also be performed at EOT if the initial bone marrow evaluation was positive and a response has been achieved but relapse is subsequently documented (optional to patients).

Table C Expansion Part (Dosing Schedule A) Sparse PK and Pharmacodynamic Assessments Schedule (a)

	Cycle 1												Cycles 2, 3, and 4
	Day 1			Day 8			Day 15			Day 22			Day 1
	PK	PD		PK	PD		PK	PD		PK	PD		PK
	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma
Predose (within 1 hour before dosing) (b)	X	X	X	X	X	X	X	X	X	X	X	X	X
2 or 4 hours postdose	X			X	X		X	X		X	X		

PD=pharmacodynamic, PBMC=peripheral blood mononuclear cell(s), PD=pharmacodynamic, PK=pharmacokinetic.
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 collection of the blood samples.
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.
(a) In the subset of Japanese patients designated for intensive PK sampling, plasma and urine PK samples and pharmacodynamic samples will be collected during Cycle 1 at time points specified in Table A (Dose Escalation Part [Dosing Schedule A] PK, ECG, and Pharmacodynamic Assessment Schedule). In addition, plasma PK samples will be collected predose on Day 1 of Cycles 2, 3, and 4 according to Table C (Expansion Part [Dosing Schedule A] Sparse PK and PD Assessments Schedule).
(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. The timing of the predose samples 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.

Table D Expansion Part (Dosing Schedule B) Sparse PK and Pharmacodynamic Assessments Schedule (a)

	Cycle 1												Cycles 2, 3, and 4
	Day 1			Day 7			Day 15			Day 21			Day 7
	PK	PD		PK	PD		PK	PD		PK	PD		PK
	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma	Serum	PBMC	Plasma
Predose (within 1 hour before dosing) (b)	X	X	X	X	X	X	X	X	X	X	X	X	X
2 or 4 hours postdose	X			X	X					X	X		

PD= pharmacodynamic, PBMC=peripheral blood mononuclear cell(s), PD=pharmacodynamic, PK=pharmacokinetic.
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 collection of the blood samples.
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.
(a) In the subset of Japanese patients designated for intensive PK sampling, plasma and urine PK samples and pharmacodynamic samples will be collected during Cycle 1 at time points specified in Table B (Dose Escalation Part [Dosing Schedule B] PK, ECG, and Pharmacodynamic Assessment Schedule). In addition, plasma PK samples will be collected predose on Day 7 of Cycles 2, 3, and 4 according to Table D (Expansion Part [Dosing Schedule B] Sparse PK and PD Assessments Schedule).
(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. The timing of the predose samples 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.

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 investigator agrees to assume the following responsibilities:

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 subjects, 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 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 subjects. 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 ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
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. This responsibility lies on the appropriate individual, designated by the site in Japan.
13. Report adverse reactions 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.

The 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 the 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 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.

The 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 the investigator's own country.

The 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 International Working Group 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, immunohistochemistry 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; 1 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 but no 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 [25].
CR=complete remission, FDG=[^{18}F]fluorodeoxyglucose, PET=positron emission tomography, CT=computed tomography, PR=partial remission, SPD=sum of the product of the diameters, SD=stable disease, PD=progressive disease.

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, 1982.

Appendix F Cockcroft-Gault Equation

For male subjects:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})} \text{ OR } \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [μmol/L]})}$$

For female subjects:

$$\text{Creatinine clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})} \text{ OR } \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [μmol/L]})}$$

Source: Cockcroft DW and Gault MH, 1976.

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 as 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 subject.
(5) A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix H New York Heart Association Classification of Functional Capacity

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.

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 azithromycin boceprevir captopril carvedilol cyclosporine daclatasvir diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole nefazodone posaconazole quercetin quinidine ranolazine simeprevir ticagrelor velpatasvir + sofosbuvir (fixed dose combination) verapamil voriconazole	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)
Strong CYP3A Mechanism-Based Inhibitors	
clarithromycin (c) conivaptan (c) danoprevir + ritonavir (c) mibefradil (c) paritaprevir + ritonavir + ombitasvir (fixed dose combination) (c) paritaprevir + ritonavir + ombitasvir + dasabuvir (fixed dose combination) (c) telaprevir (c) telithromycin	7 days, or 5 times the inhibitor half-life, whichever is longer
grapefruit and grapefruit-containing foods and beverages	5 days

Footnotes are on last table page.

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

Medication, Supplement, or Food Product (a) (b)	Required Washout Period Before First Dose
Strong CYP3A Inducers and/or P-gp Inducers	
avasimibe carbamazepine phenobarbital phenytoin primidone rifabutin rifampin rifapentine St. John's wort	7 days, or 5 times the inducer half-life, whichever is longer

(a) Note the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm) If a medication, supplement, or food/beverage is suspected or known to be a or 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 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 are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.
(c) Also inhibitors of P-gp.

Appendix J Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the major changes in Amendment 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: Revised the planned number of sites.

The primary change occurs in Section 2.0 STUDY SUMMARY.

Amended text:

Planned Number of Sites:

Dose escalation part: approximately 3-**5** sites

~~DLBCL e~~**E**xpansion part: approximately 6-**10** sites

Rationale for Change:

To add flexibility to the number of sites to take part in this study considering the recruitment prediction with addition of new cohorts and change in targeted tumor type in expansion part.

Change 2: Updated the diseases under study section to include FL and MZL.

The primary change occurs in Section 4.1.1 Diseases Under Study. New references are added, and reference numbers revised accordingly.

Amended text:

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of lymphoproliferative disorders originating in B lymphocytes, T lymphocytes, or natural killer (NK) cells. Mature B-cell lymphomas account for greater than 85% of NHL cases worldwide~~, and its major subtype is~~. **The two most common types of NHL are** diffuse large B-cell lymphoma (DLBCL) **and follicular lymphoma (FL)** [1]. NHL is one of the most common malignancies worldwide, with an estimated 386,000 new cases and 200,000 deaths in 2012. The incidence of NHL exhibits marked geographic variation and is higher in North America and Europe. The East Asia region has one of the lowest incidence rates. While the increasing incidence of malignant lymphoma has recently slowed in Western countries, other parts of the world, including East Asia, have continued to experience an upward trend. In 2012, an estimated 63,000 people in the United States (US), 34,000 people in Western Europe, and 72,000 people in East ~~Asian~~**Asia** (21,000 Japanese; 43,000 Chinese; and 4,700 South Korean) were diagnosed with NHL [2].

In East Asia, it is the same tendency with the Western countries that B-cell neoplasms are the most common followed by T/NK cell neoplasms. The proportion of mature B-cell and T/NK cell lymphoma subtypes is different, while the most common subtype is DLBCL in China, Korea and Japan. Japan shows a higher proportion of FL and adult T-cell leukemia/lymphoma cases, and China has a higher proportion of extranodal NK/T-cell lymphoma, nasal type cases [3]. In Korea, precursor cell neoplasms are relatively high and MZL is the

second most common subtype among mature B-cell lymphoma [4].

4.1.1.1 DLBCL

DLBCL represents about 30% of all NHL. It is estimated that approximately 20,000; 10,000; 6,400; 12,000; and 1,400 new cases of DLBCL are diagnosed annually in the United States, Western Europe, Japan, China, and South Korea, respectively [27]. DLBCL is a form of aggressive B-cell NHL that is invariably fatal without treatment.

…

4.1.1.2 Indolent NHL

Follicular lymphoma (FL) is the most common indolent NHL in the Western hemisphere, representing 20% of NHL [12]. Randomized clinical trials have demonstrated that the addition of rituximab to standard chemotherapy induction has improved overall survival. Maintenance rituximab strategies can improve PFS. Bendamustine combined with rituximab has rapidly become a standard frontline strategy in North America and parts of Europe. However, several unmet needs remain, including the identification of high-risk patients at diagnosis and the development of predictive biomarkers for targeted agents [12].

Other common B cell malignancies include Mantle cell lymphoma (MCL) and MZL. These B cell lymphoma subtypes comprise about 6% and 10% of all NHL respectively [13]. In Asia, the proportion of MCL and MZL is 2.4%, 8.3% in China, 1.8%, 13.5% in Korea and 3.3%, 4.3% in Japan of total lymphoid neoplasms [3]. MCL is poor prognostic despite the development of therapeutic strategy based on understanding of its biology and is thought to have the worst characterstics of both indolent and aggressive NHLs [14]. MZL is heterogeneous and clinocopathological subtypes are extranodal MZL of MALT, nodal MZL and splenic MZL[13].

For indolent B-NHL, watchful wait or radiotherapy is frequently used for early stage or low-tumor burden lymphoma, while rituximab or rituximab plus cytotoxic agent(s) such as CHOP, bendamustine is administer for patients who require chemotherapy [15][16]. In Japan, R-CHOP or R-Bendamustine is frequently chosen as the frontline treatment for FL and MZL [17][18][19]. In relapsed or refractory iNHL, bendamustine as a single agent or rituximab-containing chemotherapy regimens can be used.

In Korea, R-CVP (cyclophosphamide, vincristine, prednisolone) is used for MZL [20], and R-CVP and R-CHOP are used for FL [21].

Rationale for Change:

To provide information on the new target tumor types for the expansion part.

Change 3: Added a sentence to the nonclinical experience section to instruct the reader to refer to the TAK-659 IB for detailed discussion of the nonclinical toxicology, metabolism, and pharmacology of TAK-659.

The primary change occurs in Section 4.1.3 Nonclinical Experience.

Amended text:

Overall, the nonclinical safety profile of TAK-659 has been adequately characterized. The nonclinical assessment of TAK-659 supports clinical trials in patients with advanced malignancies such as relapsed and/or refractory ~~DLBCL~~ **FL**.

A detailed discussion of the nonclinical toxicology, metabolism, and pharmacology of TAK-659 can be found in the TAK-659 IB.

Rationale for Change:

To clarify where further information can be found.

Change 4: Updated the clinical experience section with more recent data.

The primary change occurs in Section 4.1.4 Clinical Experience.

Amended text:

~~As of 27 April 2016, 68 patients have been dosed with TAK-659, including 54 patients in the first-in-human (FIH) Study C34001 and 14 patients in Study C34002.~~

*4.1.4.1 Clinical ~~Safety and Efficacy of~~ **Experience with** TAK-659*

TAK-659 **is being investigated in 7 clinical studies involving patients with advanced malignancies (Table 4.a) in addition to this study. The status of each study is described below.**

~~In Study C34001, an open-label, multicenter, phase 1, dose escalation study of TAK-659 in adult patients with advanced solid tumors and lymphoma malignancies, the TAK-659 dose was escalated from 60 mg to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [14 patients], and 120 mg [7 patients]). The maximum tolerated dose (MTD) for patients with lymphoma and solid tumors has been determined to be 100 mg once daily (QD). The patients in the expansion phase of the study are treated at the MTD/recommended phase 2 dose (RP2D) of 100 mg. Of the 54 patients treated in this study (35 lymphoma, 18 solid tumors, and 1 chronic lymphocytic leukemia [CLL]), 40 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included PD (20 patients), adverse events (AEs) (9 patients), withdrawal of consent (1 patient), protocol violation (1 patient), symptomatic deterioration (3 patients), and other (6 patients).~~

~~In Study C34002, an open-label, multicenter, phase 1b/2, dose escalation and expansion study of TAK-659 in adult patients with relapsed or refractory AML, the TAK-659 dose has been escalated from 60 mg to 100 mg to 120 mg (4 patients, 7~~

~~patients, and 3 patients, respectively). Of the 14 patients treated in this study, 11 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included AEs (7 patients), PD (2 patients), withdrawal by subject (1 patient), and other (1 patient).~~

~~The reported AEs were generally as expected based on nonclinical toxicology findings of TAK-659 and the patient population being studied. In Study C34001, 10 deaths were reported. The causes of the deaths included sepsis, PD (3 patients each), hypoxia, pulmonary embolism, hepatic encephalopathy and pneumonia (1 patient each). One of the AEs that led to death (sepsis) was considered treatment related. The most common treatment-related AEs reported in Study C34001 (≥20% of patients) have been aspartate aminotransferase (AST) increased (23 patients [43%]), fatigue (15 patients [28%]), amylase increased (12 patients [22%]), lipase increased (12 patients [22%]), and diarrhea (11 patients [20%]). The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been hypophosphatemia (7 patients [13%]), amylase increased (6 patients [11%]), anemia (5 patients [9%]), neutropenia (5 patients [9%]), lipase increased (4 patients [7%]), and pneumonia (3 patients [6%]). As noted, Grade 3 or greater treatment-related increased serum lipase was observed in 4 patients (7%), and Grade 3 or greater treatment-related increased AST was observed in 2 patients (4%). However, patients did not have any related symptoms, nor was there evidence of pancreatitis or other tissue injuries. Further investigations are required to determine the clinical significance of these asymptomatic laboratory abnormalities.~~

~~In Study C34001, of the 26 response-evaluable patients with lymphoma, 11 patients had responded to treatment according to investigator reports. Five patients with DLBCL achieved a partial response (PR) and 3 achieved a CR. Three patients with FL achieved PRs.~~

Currently, more than 300 patients have been dosed with TAK-659, including 143 patients in first-in-human (FIH) Study C34001 (single-agent study in advanced solid tumors and lymphomas), 43 patients in Study C34002 (single-agent study in relapsed or refractory AML), 41 patients in Study C34003 (study of TAK-659 in combination of nivolumab in advanced solid tumors), 49 patients in Study C34004 (single-agent study in DLBCL), 41 patients in Study C34005 (study of TAK-659 in different combinations in NHL), 10 patients in Study C34007 (single-agent dose escalation study in Japanese patients), and 11 patients in Study C34008 (study of TAK-659 in combination with venetoclax in NHL). Further details about safety and efficacy on these clinical studies are provided in the current IB.

For detailed clinical study information, please refer to the TAK-659 IB.

[A new table (Table 4.a Overview of TAK-659 Clinical Studies) added]

…

4.1.4.2 Clinical PK of TAK-659

~~As of 27 April 2016, clinical PK data include preliminary data from the dose escalation portion of Study C34001, an ongoing, phase 1, FIH, dose escalation and expansion study in patients with advanced solid tumors or lymphomas. Preliminary PK results from Study C34001 are available across the 60 to 120 mg QD dose range in patients with solid tumors and lymphoma enrolled at US clinical study sites. 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). Because Study C34007 will enroll patients with NHL only, PK results below are summarized specifically for NHL patients.~~

~~Among patients with relapsed/refractory lymphoma, TAK-659 exhibited fast absorption after oral administration of an immediate-release tablet formulation (~~**Preliminary plasma pharmacokinetics (PK) results are available from lymphoma, solid tumor, and AML patients enrolled in Studies C34001 and C34002. In addition, preliminary urine PK results are available from lymphoma and solid tumor patients enrolled in the dose escalation cohorts of Study C34001. TAK-659 is characterized by fast absorption (overall** 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, as determined by a comparison of predose (trough) concentrations available during Cycle 1. Geometric mean values of steady-state dose-normalized~~ **) in patients with hematologic and nonhematologic malignancies. Moderate variability is observed among dose-normalized steady-state AUC_{τ} (**area under the plasma concentration-time curve ~~over~~**during** the dosing interval ~~(AUC_{τ}/Dose) were similar across the 60 to 100 mg 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~~**) values in lymphoma, solid tumor, and AML patients** (coefficient of variation ~~[CV] of 30% for Day 1 and 50% for Day 15).~~

~~Following repeated QD dosing, TAK-659 was characterized by mean~~**of 20.0%, 43.5%, and 34.8%, respectively). An approximately dose-proportional increase in steady state AUC_{τ} was observed over the 60 to 160 mg range in patients with AML. Mean** accumulation ~~of 2.1~~**ratios ranging from 1.90-**fold~~. The~~ **to 2.54-fold and** 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~~**ratios ranging from 4.34 to 5.09 were observed across the study populations after repeated QD dosing for 15 days. Based on data in lymphoma and solid tumor patients,** renal clearance ~~to~~**accounted for about 30%**

of TAK-659 apparent ~~oral~~ clearance ~~was 0.34. Although the exact contribution of renal excretion~~**, and therefore at least about 30%** 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 was 3.9-fold higher than estimated glomerular filtration rate (based on creatinine clearance calculated by the Cockcroft-Gault equation), suggesting that active~~**. Active** tubular secretion ~~is~~**appeared to be** the ~~major~~**predominant** component of renal clearance**, based on comparison of unbound renal clearance to glomerular filtration rate**. ~~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%-73.0%) of TAK-659 metabolism in human liver microsomes, with relatively minor contributions by CYP2D6 (16.6%-30.9%) and CYP1A2 (0%-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~~. **Geometric mean terminal disposition half-life of 34.4 hours was determined in a single dose PK run-in phase of the indolent NHL expansion cohort of Study C34001.**

Refer to the TAK-659 IB for detailed clinical pharmacology information.

Rationale for Change:

To update values on the basis of newer clinical data.

Change 5: Updated the risks and benefits section with more recent data.

The primary change occurs in Section 4.1.5 Risks and Benefits.

Amended text:

Because TAK-659 has been administered to ~~a total~~**limited number** of ~~only 68~~ patients ~~as of 27 April 2016~~, it is not currently possible to identify and describe with certainty the adverse effects of the compound.

…

4.1.5.2 Potential Risks Based on Clinical Observations

~~On~~**As of** the ~~basis of data from Study C34001,~~ **22 October 2017 data cutoff, following evaluation of the current safety data,** asymptomatic **lipase** elevation ~~in lipase was added~~**, pneumonitis, and infections (including pneumonia, CMV infections, and sepsis) are recognized** 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.~~ **potential risks.**

Asymptomatic Lipase Elevation

In clinical studies to date, ~~asymptomatic~~ lipase ~~or amylase~~ elevations are reported commonly (≥10%). Patients in S~~s~~tudy C34007 will have frequent monitoring of lipase and amylase as outlined in the Schedule~~s~~ of Events (Appendix A).

Pneumonitis

Cases of pneumonitis have been reported in clinical studies with **B-cell receptor (**BCR**)** pathway kinase inhibitors, including TAK-659, and pneumonitis is considered ~~an important~~**a** potential risk of TAK-659. **There were 5 SAEs of pneumonitis (4 reported in C34001 and 1 reported in C34002).** Pneumonitis and other pulmonary toxicities are being closely ~~monitored in TAK-659 clinical studies and will also be closely monitored~~**monitor patients for respiratory signs and symptoms throughout TAK-659 treatment.**

Infections

In an analysis of safety data from 107 patients with lymphoma treated with single-agent TAK-659 in Study ~~C34007~~**C34001, most patients (72%) experienced at least 1 TEAE of any grade classified under the infections and infestations System Organ Class (SOC) as defined by the Medical Dictionary for Regulatory Activities (MedDRA). Pneumonia was the most frequently reported infection TEAE (26%) and most frequently reported infection SAE (15%). CMV infection (20%) and sepsis (17%) were also frequently reported infection TEAEs. Sepsis (17%) and pneumonia (15%) were the most frequently reported ≥ Grade 3 infection TEAEs. In a heavily pretreated relapsed and/or refractory lymphoma patient population, a high rate of infection is expected particularly when considering confounding factors such as comorbidities or other immunosuppressive medications. The rate of infection, including pneumonia and sepsis, observed in patients with lymphoma who received TAK-659 is high and warrants continued monitoring and/or prophylaxis as outlined by this protocol.**

Refer to the TAK-659 IB for detailed information on potential risks.

4.1.5.3 Drug-Drug Interaction Risk Assessment

…

~~In cell-based assays, TAK-659 was not a substrate of the efflux transporter breast cancer resistance protein (BCRP), or the uptake transporters organic anion transporter (OAT)1, OAT3, organic cation transporter 2 (OCT2), organic anion-transporting polypeptide (OATP)1B1, or OATP1B3. Therefore, there is low risk for inhibitors or inducers of these transporters to affect TAK-659 exposure.~~

…

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

4.1.5.4 Potential Benefits Based on Clinical Observations

The benefits of TAK-659 have not been established; however~~, early~~ **the clinical benefit of TAK-659 has been and continues to be investigated as a single agent or in combination with other agents for the treatment of patients with advanced solid tumors, NHL, and AML. Early** signs of clinical antitumor activity were seen~~. In Study C34001, as of the 27 April 2016 data cutoff, 11 of 26 response-evaluable patients with lymphoma responded to treatment (8 with DLBCL and 3 with FL). Five patients with DLBCL achieved a PR and 3 achieved a CR, and 3 patients with FL achieved a PR~~.

Clinical benefit has been observed in First In Human Study C34001 evaluating TAK-659 as a single agent. Response data were available for 106 patients (11 solid tumor, 69 DLBCL, 17 indolent NHL, 5 Chronic Lymphocytic Leukemia [CLL]), 3 Mantle Cell Lymphoma (MCL), and 1 Post Transplant Lymphoproliferative Disorder (PTLD) as of 22 October 2018 in Study C34001. Among response-evaluable patients with solid tumors, 1 patient (9%) experienced a partial response (PR). Among response-evaluable patients with DLBCL, best responses of CR and PR were reported for 14 and 12 patients, respectively. Among the 5 response-evaluable patients with CLL, 3 patients achieved PR. Thirteen patients with indolent lymphomas responded to treatment with TAK-659. Four patients achieved a CR and 9 patients achieved PR. These indolent responders were made up of both Follicular and Marginal Zone Lymphoma patients. Lastly, 1 out of 3 patients with MCL achieved a PR.

Additional single agent activity was observed in Studies C34004, a phase 2 R/R DLBCL study and this study, C34007. Of 41 response evaluable DLBCL patients in C34004, 8 responded. Three out of 4 DLBCL and 2 out of 2 FL patients responded in C34007.

Responses have also been observed in two additional NHL studies where TAK-659 was combined with other agents. Fifteen out of 29 response evaluable NHL patients responded in Study C34005, a five-arm combination study with more than half of patients enrolled into the Bendamustine +/- Rituximab arms. Four of out 5 response evaluable NHL patients responded in Study C34008, a Phase 1b study of TAK-659 in combination with venetoclax.

Specific details of the tumor response by cancer type can be found in the TAK-659 IB.

Rationale for Change:

To update values on the basis of newer clinical data.

Change 6: Revised the rationale for the proposed study.

The primary change occurs in Section 4.2 Rationale for the Proposed Study.

Amended text:

This study is intended to evaluate the safety, tolerability, PK, and efficacy of single-agent TAK-659 in East Asian patients with NHL and to expand the TAK-659 global clinical development program to the East Asian population.

The TAK-659 MTD and RP2D in Western patients with lymphoma were determined in the FIH study (C34001) to be 100 mg QD in 28-day treatment cycles. Objective responses have been observed in patients with lymphoma (DLBCL, **iNHL [FL** and ~~FL~~**MZL], CLL, and MCL**) across the multiple dose levels evaluated (60-120 mg QD), supporting further evaluation of TAK-659 in relapsed and/or refractory ~~DLBCL~~**FL or MZL** after at least 2 prior lines of chemotherapy; a setting that represents an unmet medical need in which there is no standard of care available.

In addition, on the basis of the currently available data, TAK-659 ~~has demonstrated a manageable safety and tolerability profile.~~**administration can lead to adverse events (AEs) that are generally manageable and reversible with dose modification and/or prophylactic/supportive care.** AEs reported in the clinical studies to date are consistent with nonclinical toxicology findings of TAK-659, published studies of other BCR pathway inhibitors ~~[10] [11] [12]~~ **[22] [23] [24]**, and the patient population being studied. These events are detectable using standard safety monitoring practices and **are generally** manageable in the clinical setting.

These results support the initiation of an Asian phase 1 study, including a dose escalation part to determine the MTD and/or RP2D and PK profile of TAK-659 in East Asian patients with NHL and a dose expansion part to further evaluate the safety and investigate preliminary efficacy in patients with relapsed and/or refractory ~~DLBCL~~**FL/MZL**.

Rationale for Change:

To update the target tumor type in the expansion part from DLBCL to FL/MZL in line with the rationale described in section 1.3.1.

Change7: Revised the rationale for dose and dosing schedule.

The primary change occurs in Section 4.2.1 Rationale for Dose and Dosing Schedule.

Amended text:

4.2.1 Rationale for Dose and Dosing Schedule

Because this is the first clinical study of TAK-659 in Asia, the initial dose and dose increment will be determined on the basis of the starting dose and MTD from the FIH study (C34001) conducted in Western patients.

~~As of 27 April 2016, 54 patients had been dosed with TAK-659 in Study C34001. Of the 54 patients dosed, 35 were dosed in the escalation part (18 solid tumor, 12 DLBCL, 4 FL, and 1 MCL), and 19 had been dosed in the expansion part (18 DLBCL~~

~~and 1 CLL). During the dose escalation part of the study, the TAK-659 dose was escalated from 60 to 120 mg QD (60 mg [10 patients], 80 mg [4 patients], 100 mg [14 patients], and 120 mg [7 patients]). No dose-limiting toxicities (DLTs) were observed in the 14 patients (including 8 DLT-evaluable patients) dosed at 100 mg in the dose escalation part. The MTD/RP2D for patients with lymphoma was determined to be 100 mg QD. Nineteen patients in the expansion cohorts had received TAK-659 at the 100 mg QD dose. In total, 33 patients had been dosed at 100 mg QD. Longer-term safety and tolerability data of the 100 mg QD dose is limited at the present time, but will be further collected in the ongoing and planned studies. However, based on the currently available data, the benefit/risk assessment for the 100 mg QD dose is favourable.~~

~~Although the metabolic and disposition profiles of TAK-659 remain to be fully characterized in humans, the relative contribution for each CYP (CYP3A4, CYP2D6, and CYP1A2) to the overall human liver microsomal metabolism was estimated to be 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.4%, respectively, from in vitro data, suggesting that TAK-659 is predominantly metabolized by CYP3A, with minor contributions by CYP2D6 and CYP1A2. TAK-659 is also a substrate for P-gp but not for uptake transporters such as OATP1B1 and OATP1B3. Genetic differences in CYP3A and P-gp are not known to be associated with clinically meaningful differences in exposure. From the preliminary results in Study C34001, 34% of the orally administered TAK-659 dose was excreted into the urine as unchanged TAK-659 in patients with lymphoma. These data do not indicate a major contribution of enzymes or transporters with clinically significant genetic polymorphisms and/or interethnic differences (ie, CYP2C19, CYP2D6, hepatic OATP) to TAK-659 systemic clearance.~~

Although 100 mg QD TAK-659 has been determined to be the MTD 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 in Western patients, responses to TAK-659 were also observed in patients treated with two lower doses evaluated (60 mg and 80 mg) QD, suggesting a therapeutic window of TAK-659 extending from 60 mg to 100 mg QD. Plasma PK exposure of TAK-659 from that study 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 Western MTD of 100 mg QD and may fall at a QD dose or intermittent schedule below that. It is also possible that there may be efficacious doses below 60 mg QD which is why 40 mg QD will also be

tested. In this study, intermittent dosing schedules of TAK-659 will be also be evaluated such as 7 days on followed by 7 days off. The rationale for intermittent dosing schedules for TAK-659 is based on the occurrence of frequent dose interruptions in Cycle 1 and 2 due to various AEs that was observed in study C34001. Most of the AEs that led to drug holds were laboratory changes that returned to ≤Grade 1 with drug hold. In addition to this, most subjects in C34001 that received more than 6 cycles of treatment had multiple dose holds and dose reductions from 100 mg down to 60 mg QD. Moreover, TAK-659 intermittent regimen has been conducted in Study C34008 and showed potential of more tolerability and safety compared to daily administration in combination regimen. This study is monotherapy, however, intermittent regimen is worthwhile to explore in this study to elucidate monotherapy dose optimization.

The starting dose in this study will be 60 mg QD, which is the same as that in Study C34001, and which is 2 dose levels (40%) lower than the MTD determined in the Western patient population. If 60 mg QD is proven to be safe and tolerable, ~~dosing will increase to 100 mg QD. Subsequent escalations beyond 100 mg QD, as permitted by safety/tolerability,~~ **dose escalation** will be conducted in 20 mg increments of daily dose. **Based on emerging safety, tolerability, PK data, a lower dose (eg, 40 mg QD) or alternative dosing regimens (eg, 7 days on followed by 7 days off) will be permitted.**

Rationale for Change:

To provide rationale for the addition of 2 possible new cohorts (40 mg QD continuous and 80 mg QD 7 days on/7 days off intermittent regimen) to the dose escalation part based on current clinical data.

Change 8: Revised the rationale for PK assessments section.

The primary change occurs in Section 4.2.2 Rationale for PK Assessments.

Amended text: In the dose escalation part, intensive PK samples will be collected from all patients during Cycle 1 to permit detailed characterization of TAK-659 plasma and urine PK across different dose levels in East Asian patients with NHL (refer to Section 9.4.17.1 and Appendix A, Table A **and Table B**). Plasma PK data will be used to characterize single- and repeat-dose concentration-time profiles of TAK-659, calculate PK parameters, evaluate the dose-exposure relationship, and contribute to population PK analysis. Urine PK data will be used to determine the percentage of the administered TAK-659 dose excreted in urine as unchanged drug, and renal clearance and its minimum contribution to systemic clearance.

In the ~~DLBCL~~ expansion part, blood samples for plasma PK will be collected via a limited (sparse) sampling schedule to contribute to population PK and exposure-response analyses (refer to Section 9.4.17.2 and Appendix A, ~~Table B~~ **Table C and Table D**)

Rationale for Change:

To reflect the addition of new tables (Schedule of Events [Appendix A], Table B and Table D) regarding PK sample collection for the new dosing schedule.

CCI

Change 10: Revised target tumor type description in the secondary objective regarding evaluation of the preliminary efficacy of TAK-659.

The primary change occurs in Section 5.1.2 Secondary Objective.

Amended text:	The secondary objective is to evaluate preliminary efficacy of TAK-659 in patients with relapsed and/or refractory ~~DLBCL~~**NHL**.

Rationale for Change:

To reflect the change in the target tumor type in the expansion part.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

CCI

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 4.2.2 Rationale for PK Assessments
- CCI
- Section 5.1.3 Exploratory Objectives
- Section 5.2.4 Exploratory Endpoints
- Section 6.1 Overview of Study Design
- Schedule of Events (Appendix A), for Dose Escalation Part, footnote (y)
- Schedule of Events (Appendix A) for Expansion Part, footnote (v)

Change 12: Revised the assessment time points for the PK-related primary/additional endpoints.

The primary change occurs in Section 5.2.1 Primary Endpoints and Section 5.2.3 Additional Endpoints.

Amended text:

5.2.1 Primary Endpoints

- ~~Summary statistics of~~ TAK-659 C_{max} on Cycle 1 Days 1 and **7 or** 15 by dose.
- ~~Summary statistics of~~ TAK-659 T_{max} on Cycle 1 Days 1 and **7 or** 15 by dose.
- ~~Summary statistics of~~ TAK-659 AUC_{τ} on Cycle 1 Days 1 and **7 or** 15 by dose.

- ~~Summary statistics of r~~**R**enal clearance (CL_R) on Cycle 1 Day **7 or** 15 by dose.

5.2.3 Additional Endpoints

- ~~Summary statistics of a~~**A**pparent oral clearance (CL/F), CL_R as a percentage of CL/F, peak-trough ratio (PTR), accumulation ratio (Rac), and observed concentration at the end of the dosing interval (C_{trough}) on Cycle 1 Day **7 or** ~~15~~ by dose.

Rationale for Change:

To reflect the PK assessment dates for the new intermittent dosing schedule, and to better define the endpoints.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures, Table 6.a Primary and Secondary Endpoints for Disclosures

Change 13: Revised the name of the expansion part, and removed one of the secondary endpoints regarding the assessment of time to progression (TTP).

The primary change occurs in Section 5.2.2 Secondary Endpoints. The name of the expansion part is revised throughout the protocol.

Amended text:

- Overall response rate (ORR) in the ~~DLBCL~~ expansion part.
- CR rate in the ~~DLBCL~~ expansion part.
- Duration of response (DOR) in the ~~DLBCL~~ expansion part.
- ~~Time to progression (TTP) in the DLBCL expansion part.~~
- Progression-free survival (PFS) in the ~~DLBCL~~ expansion part.

Rationale for Change:

- The name of the expansion part was revised to reflect the change in the target tumor type in the expansion part.
- The endpoint regarding TTP was removed because PFS is a more relevant endpoint in the indolent lymphoma subtypes (FL and MZL) under study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures, Table 6.a Primary and Secondary Endpoints for Disclosures

Change 14: Removed response data collection assessed using the IWG 2014 (Lugano) criteria.

The primary change occurs in Section 5.2.2 Secondary Endpoints.

Amended text:	The investigators will perform response assessment using modified International Working Group (IWG) 2007 criteria for malignant lymphoma ~~[13]~~ **[25]**, which will be the main analysis for the efficacy endpoints. ~~In addition, response might be assessed by the investigator following the IWG 2014 (Lugano) criteria [14], and these data might be used for sensitivity analyses of efficacy endpoints.~~

Rationale for Change:

Revised because the IWG 2007 criteria is the most common criteria in Asian clinical practice.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.1 Overview of Study Design
- Section 9.4.15 Disease Assessment
- Section 13.1.3 Efficacy Analysis
- Schedule of Events (Appendix A) for Dose Escalation Part, footnote (k)
- Schedule of Events (Appendix A) for Expansion Part, footnote (l)

CCI

[redacted]

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures, Table 6.a Primary and Secondary Endpoints for Disclosures

Change 16: Revised the overview of study design.

The primary change occurs in Section 6.1 Overview of Study Design.

Amended text:

This is an open-label, multicenter, phase 1 study of TAK-659 including a dose escalation part in adult East Asian patients with NHL and an expansion part in adult East Asian patients with relapsed and/or refractory ~~DLBCL~~**NHL**.

The dose escalation part of the study will enroll approximately ~~12~~**18** to ~~23~~**32** East Asian patients diagnosed with NHL for which no effective standard treatment is available. Assuming a dropout rate of 20%, this will ensure that ~~9~~**16** to ~~18~~**28** DLT-evaluable patients are enrolled in the dose escalation part. TAK-659 will be administered continuously, QD, in 28-day treatment cycles **(Dosing Schedule A)**. Dose escalation will follow a standard 3+3 schema to determine the MTD and/or the RP2D. The initial TAK-659 dose will be 60 mg QD and will escalate to ~~100~~**80** mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. ~~Subsequent escalation (above 100 mg QD) will be in 20 mg increments (eg, 100 mg to 120 mg).~~ Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses **or regimens**, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-659.

If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion between the investigator and the sponsor. If ≥2 of 6 patients experience a DLT at ~~100~~**80** mg QD, ~~intermediate~~**alternate** dose ~~levels~~**regimens** between 60 and ~~100~~**80** mg (ie, 80 mg **7 days on 7 days off [Dosing Schedule B]**) will be evaluated **as described below**. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the totality of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. ~~If 100 mg QD dose, which is the Western MTD/RP2D, is determined to be tolerable and there is no significant difference in systemic exposure between Asian and Western patients, dose escalation could stop at 100 mg QD without further escalation to 120 mg QD.~~ Intrapatient dose escalation is

not allowed in this protocol.

An additional dosing schedule will be tested after implementation of Amendment 02:

- **Dosing Schedule B: TAK-659 will be administered QD for 7 consecutive days followed by another 7 days of rest and repeated again (ie, 7 days "on" and 7 days "off"), for a cycle duration of 28 days. The starting dose of 80 mg QD was the maximum administered dose in Dosing Schedule A (2 out of 4 patients presented a DLT in the continuous dosing regimen). However, the alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data. Dose escalation will be governed using the same standard 3+3 schema as described in Section 8.3.**

The ~~DLBCL~~ expansion part of this study will begin once the RP2D has been determined. The ~~DLBCL~~ expansion part will proceed with ~~continuous QD~~ dosing of TAK-659 at the RP2D in 28-day cycles. The patient population will consist of East Asian patients with ~~DLBCL~~**FL or MZL** who are relapsed and/or refractory after at least 2 prior lines ~~and no more than 4 prior lines~~ of chemotherapy and who ~~have experienced failure of ASCT or are not eligible~~**must be ineligible** for ~~ASCT~~**or refusal to hematopoietic stem cell transplant**. It is expected that ~~a minimum of~~ **approximately** 12 response-evaluable patients will be enrolled. Assuming a 20% dropout rate, a total of approximately 15 patients will be enrolled. The objectives of the ~~DLBCL~~ expansion part are to evaluate the longer-term safety and tolerability of TAK-659 administered at the RP2D, to characterize the PK of TAK-659, and to evaluate the preliminary efficacy of TAK-659 in relapsed and/or refractory ~~DLBCL~~**FL/MZL** as measured by ORR and other efficacy variables, including CR rate, DOR,TTP, and PFS.

At least 1 Japanese patient will be enrolled in each ~~group of 3 patients~~**cohort** in the dose escalation part. The total number of Japanese patients dosed at the RP2D (either the MTD or a lower dose as determined) will be at least 6 including the dose escalation and ~~DLBCL~~ expansion parts to ensure adequate characterization of PK and safety in Japanese patients.

On the basis of the geographic distribution of patients enrolled and emerging PK and safety data, additional patients may be added, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region. On the basis of emerging efficacy data, additional groups or patients with ~~specific subtypes of~~ ~~DLBCL~~**FL/MZL** may be added to further explore efficacy.

…

Serum~~Blood~~ samples will be collected pretreatment and posttreatment, and the levels of circulating cytokines/chemokines**/serum proteins** in serum will be measured. **Whole blood samples will be collected pretreatment during Cycle 1, and the**

levels of circulating immune cells will be measured.

…

Evaluation of disease response will be performed as described in Section 9.4.15 and the Schedule of Events (Appendix A), using the IWG 2007 modified response criteria for malignant lymphoma (Appendix D) [~~13~~**20**] based on investigator assessment. An imaging modality (eg, computed tomography [CT] with contrast and fluoro-2-deoxy-D-glucose [FDG]-positron emission tomography [PET] if appropriate) will be used to follow sites of measurable disease during the study treatment. ~~If investigator assessment of response following the IWG 2014 (Lugano) criteria [14] is also available per institute practice, these data will also be collected. Central collection of images at imaging time points by the sponsor or designee is required for patients in the DLBCL expansion part (optional for patients in the dose escalation part).~~**Radiographic images will be maintained at the site. Based on efficacy data observed, the sponsor can elect to have central collection of disease assessment images. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.**

The study design is detailed in Figure 6.a.

[Figure 6.a (Overview of Study Design) revised.]

Rationale for Change:

- To describe the addition of the new cohorts.
- To describe the change in the target tumor type in the expansion part.
- To reflect the change in the number of patients to be enrolled.
- CCI [redacted]
- To clarify the handling procedures of radiographic/electronic images used for reponse assessment.

Change 17: Revised the number of subjects to be enrolled into this study.

The primary change occurs in Section 6.2 Number of Patients.

Amended text:	It is expected that approximately ~~27~~**33** to ~~38~~**47** patients will be enrolled in this study from approximately 6 **to 10** study ~~centers~~**sites** in East Asia. Enrollment is defined as the time of administration of the first dose of study drug. For the dose escalation part, approximately ~~9~~**16** to ~~18~~**28** DLT-evaluable patients will be enrolled; assuming a 20% dropout rate, approximately ~~12~~**18** to ~~23~~**32** patients will be enrolled. For the ~~DLBCL~~ expansion part, ~~at least~~**approximately** 12 response-evaluable patients will be enrolled; assuming a 20% dropout rate,

approximately 15 patients will be enrolled.

Rationale for Change:

To reflect the change in patient number based on the addition of the new cohorts, and to add flexibility to the number of patients to be enrolled into the expansion part.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY
- Section 6.1 Overview of Study Design
- Section 13.3 Determination of Sample Size

Change 18: Revised the end of study/study completion definition and planned reporting section.

The primary change occurs in Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting.

Amended text:

Primary Completion/Study Completion

The primary analysis for safety, PK, and efficacy 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 4**-6** cycles of treatment with study drug and patients who discontinued study treatment must complete safety follow-up. **The estimated time frame for primary completion is approximately 47 months.** For patients enrolled in the ~~DLBCL~~ expansion part, PFS follow-up will occur every 2 months after the last dose of study drug for up to 6 months or until PD, whichever occurs first (for patients who discontinue for reasons other than PD). The estimated time frame for study completion is approximately ~~39~~**52** months.

~~Completion of the study will be considered when PFS events have occurred in 70% of the DLBCL expansion patients, or 24 months after last patient in, whichever occurs earlier. The study may be prematurely terminated if, in the opinion of the sponsor, there is sufficient reasonable cause.~~ A CSR addendum will be provided to describe additional data not included in the original CSR.

Rationale for Change:

To reflect the addition of the new cohorts to the dose escalation part and the change in target tumor type in the expansion part. Also, to reflect the change in the study reporting plan.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 19: Revised maximum time frames for the primary/secondary endpoints.

The primary change occurs in Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures.

Description of change: The maximum time frame shown in Table 6.a (Primary and Secondary Endpoints for Disclosures) for safety/efficacy-related primary/secondary endpoints were revised.

Rationale for Change:

Revised for more accuracy.

Change 20: Revised the total study duration.

The primary change occurs in Section 6.3.4 Total Study Duration.

Amended text: It is anticipated that this study will last for approximately ~~39~~**52** months, including approximately ~~26~~**27** months for the dose escalation part and approximately ~~19~~**25** months for the ~~DLBCL~~ expansion part **including 6 cycles treatment and 6 months PFS follow-up**.

Rationale for Change:

To reflect the addition of new cohorts to the dose escalation part.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 21: Revised inclusion criterion #3.

The primary change occurs in Section 7.1 Inclusion Criteria.

Amended text:

3. To be enrolled in the ~~DLBCL~~ expansion part, patients must meet the following criteria:

   a) Patients must have pathologically confirmed ~~DLBCL, including de novo~~ or ~~transformed disease from indolent NHL~~**FL (Grade 1, 2, or 3A) or MZL**.

   - ~~Patients with transformed DLBCL must meet 2016 World Health Organization (WHO) criteria for DLBCL [26] on last biopsy before study entry and have ≥1 prior histological diagnosis of FL~~ or ~~other indolent disease.~~
   - ~~Patients must have 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 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 [27]) 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).

v. FL Grade 3B.

- 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.

b) Relapsed and/or refractory to ≥2 prior lines of chemotherapy based on standard of care that include at least~~:~~ **1 anti-CD20-based regimen, as well as alkylating agents (eg, cyclophosphamide or bendamustine).**

- The standard first-line chemotherapy regimen containing rituximab and an anthracycline (eg, R-CHOP) or equivalent if anthracycline is contraindicated, and

- One additional systemic chemotherapy as a second-line salvage therapy that may have included ASCT.

  i. Included are ASCT-eligible patients for whom ASCT failed following response to a standard salvage regimen, or patients who did not respond to salvage therapy and were therefore not indicated for ASCT, or patients 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.~~

c) ~~Patients should not have experienced failure of more than 4 prior lines of therapy.~~ **Patients must be ineligible for or refusal to hematopoietic stem cell transplant.**

- ~~Pre-induction salvage chemotherapy and ASCT should be considered 1 therapy.~~
- ~~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 (ie, R-CHOP+rituximab maintenance should be considered as 1 line therapy).~~
- ~~Antibody therapy given as a single agent should be considered 1 therapy.~~
- ~~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.~~

d) 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.

e) 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 a nodal mass, or ~~≥~~>1.0 cm in the longest diameter for an extranodal disease) as assessed on cross-sectional imaging by CT scan/magnetic resonance imaging (MRI). (CT scan is to be performed with contrast unless it is medically contraindicated.)

Rationale for Change:

- To reflect the change in the target tumor type in the expansion part.
- Corrected per the IWG 2007 criteria.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 22: Revised inclusion criterion #6.

The primary change occurs in Section 7.1 Inclusion Criteria.

Amended text:

6. Patients must have adequate organ function, including the following:
   a) Bone marrow reserve: absolute neutrophil count (ANC) ≥1,000/mm^3, platelet

count ≥75,000/mm^3 (≥50,000/mm^3 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 function: total bilirubin ≤1.5×the upper limit of normal range (ULN), alanine aminotransferase (ALT) and AST ≤2.5×ULN.

c) Renal function: creatinine clearance ≥60 mL/min as estimated by the Cockcroft-Gault equation (refer to Appendix F) ~~or based on urine collection (12 or 24 hours).~~

Rationale for Change:

To unify the method for measuring renal function. Renal function has been identified as a significant factor impacting TAK-659 exposure and there are always slight differences of creatinine clearance values based on Cockcroft-Gault equation vs urine collection.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 23: Revised exclusion criterion #9.

The primary change occurs in Section 7.2 Exclusion Criteria.

Amended text:

9. Known hepatitis B surface antigen (HBsAg) positive, or known or suspected active hepatitis C virus (HCV) infection.
   Note: **Hepatitis testing will be performed as specified in the Schedule of Events (Appendix A).** Patients who have positive hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) can be enrolled but must have an undetectable hepatitis B virus (HBV) viral load. Patients who have positive hepatitis C virus antibody (HCVAb) must have an undetectable HCV viral load.

Rationale for Change:

For clarification.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY

Change 24: Revised study drug administration section.

The primary change occurs in Section 8.1 Study Drug Administration.

Amended text:

The study drug will be ~~dosed~~**administered according to the assigned dosing schedule (ie, Dosing Schedule A or B). For Dosing Schedule A, the study drug will be administered** continuously, QD, in 28-day cycles. **For Dosing Schedule B, the study drug will be administered QD for 7 consecutive days followed by 7 days of rest and repeated again for a 28-day cycle (ie, 7 days "on" and 7 days "off").** 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.

Rationale for Change:

To reflect the addition of a new dosing schedule.

Change 25: Clarified the definitions of DLT.

The primary change occurs in Section 8.2 Definitions of DLT.

Amended text:

Toxicity will be evaluated according to the NCI CTCAE, version 4.03, effective 14 June 2010[~~17~~**28**]. These criteria are provided in the Study Manual. DLT is defined as any of the following events **occurring during Cycle 1** that are considered by the investigator to be at least possibly related to therapy with TAK-659 ~~(note that AEs for which the relationship to study drug cannot be ruled out should be considered possibly related to study drug)~~.

…

- Receiving <75% of planned doses of study drug **(receiving <21 days for Dosing Schedule A and <11 days for Dosing Schedule B)** within Cycle 1 because of prolonged treatment interruption caused by TAK-659-related toxicities.

Although ~~DLTs~~**DLT-like toxicities** may occur at any time during treatment, only DLTs occurring during Cycle 1 of treatment will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored throughout all cycles of therapy for treatment-related toxicities.

Rationale for Change:

- To clarify that related AEs which meet the DLT criteria will only be judged as DLTs when they occur during Cycle 1. DLT definition is important for the study, but the definition was unclear in the previous version of the protocol.
- Removed the "note" in parenthesis for consistency with the definition of relationship of AEs with the study drug in Section 10.2.
- To clarify the exact number of days needed for the subject to receive 75% of planned doses in both dosing schedules.
- To clarify the difference in DLTs and DLT-like toxicities.

Change 26: Updated the dose escalation rules section.

The primary change occurs in Section 8.3 Dose Escalation Rules.

Amended text:

Dose escalation will follow a standard 3+3 schema to determine the MTD and/or the RP2D in East Asian patients with NHL. The dose escalation plan, as specified in Table 8.a, is based on the starting dose of 60 mg, the dose determined to be tolerable in

the FIH Study C34001 in the Western population. The dose will escalate to ~~100~~**80** mg QD provided that the safety and tolerability of the 60 mg dose has been demonstrated. ~~Subsequent escalation (above 100 mg QD) will follow in 20 mg increments (eg, 100 mg to 120 mg).~~ Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses **or regimens**, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-659. If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion between the investigator and the sponsor. If ≥2 of 6 patients experience a DLT at ~~100 mg QD, intermediate dose levels between 60 and 100 mg (ie, 80 mg) will be evaluated. If 100 mg QD dose, which is the Western MTD/RP2D, is determined to be tolerable and there is no significant difference in systemic exposure between Asian and Western patients, dose escalation could stop at 100 mg QD without further escalation to 120 mg QD~~**80 mg QD, alternate dose regimens between 60 and 80 mg (ie, 80 mg 7 days on 7 days off) will be evaluated.**

…

Table 8.a Planned Dose Levels

Dose Level	Dose (unit)
1	60 mg **QD**
2	~~100~~**80** mg **QD**
3	~~120~~**40** mg **QD**
4	**80 mg QD*, 7 days on/7 days off**

***The alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data.**

More conservative dose escalation, evaluation of intermediate doses **or alternative regimens**, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationship of TAK-659.

DLT-evaluable patients in each dose cohort will consist of patients who have met the minimum treatment and safety evaluation requirements of the study or who have experienced a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days **for Dosing Schedule A and for ≥11 days for Dosing Schedule B** (receiving at least 75% of planned doses of TAK-659 in Cycle 1) and observed for ≥28 days following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data

by both the sponsor and investigators to conclude that a DLT did not occur. …

Rationale for Change:

To reflect the addition of the new cohorts in the dose escalation part and to update based on latest clinical experience.

Change 27: Added a table showing dose reduction levels for TAK-659.

The primary change occurs in Section 8.4.1 General Principles. Also, the numbering of the original Table 8.b (TAK-659 Dose Adjustments for Hematologic Toxicities) and Table 8.c (TAK-659 Dose Adjustments for Nonhematologic Toxicities) have been revised to Table 8c and Table 8.d, respectively.

Amended text: …Patients who have a TAK-659 dose held because of a treatment-related or possibly related AE may resume study drug after resolution of the AE, and may either maintain the same dose level or have TAK-659 reduced by at least 1 dose level (dose reduction). **Dose reduction levels for TAK-659 are presented in Table 8.b.** When a dose reduction occurs, the TAK-659 dose will be reduced to the next lower dose. If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 can be further reduced if the treating physician believes that the patient is benefiting from study treatment and may benefit at a further-reduced dose of TAK-659. When a dose reduction of TAK-659 is required because of toxicity, no dose re-escalation will be permitted. 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 more than 2 dose reductions **(more than 1 dose reduction for 40 mg QD)** are required in a patient, the patient should be discontinued from study treatment, unless the treating physician believes that the patient may benefit from continued study treatment after resolution of AEs to ≤Grade 1 or baseline. …

Table 8.b Dose Reduction Levels for TAK-659

Dose Reduction Levels	Dose (unit)
Planned dose	40, 60, or 80 mg
(-) 1 dose level	Planned dose minus 20 mg (a)
(-) 2 dose level	Planned dose minus 40 mg (a) (b)

(a) Intermittent regimen (eg, 7 days on/7 days off) may be allowed.
(b) Not applicable to 40 mg QD cohort.

Rationale for Change:

To clarify the dose reduction levels possible for TAK-659.

Change 28: Updated the criteria for beginning or delaying a subsequent treatment cycle.

The primary change occurs in Section 8.4.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle.

Amended text:	TAK-659 is administered in continuous cycles; therefore~~,~~ study drug should be administered continuously **or according to the intermittent dosing regimen,** unless AEs occur that meet the dose modification criteria outlined below. **Before starting a new treatment cycle, TAK-659-related AEs or laboratory abnormalities must have returned to ≤Grade 1 or baseline levels.**

Rationale for Change:

For clarification of the criteria. Also, minor revision was made to reflect the new dosing regimen.

Change 29: Clarified that the use of excluded medications to manage AEs will require appropriate washout period before resuming the study drug.

The primary change occurs in Section 8.5 Concomitant Medications and Procedures.

Amended text:	… If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted due to that AE, the medications listed above and in Appendix I may be used for AE management provided there is no appropriate alternative treatment available based on 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.~~**Treatment with the study drug may then resume after an appropriate washout period for the prohibited concomitant medication (consistent with the washout period as specified in the eligibility criteria for the study). Sites are encouraged to discuss any such situations with the Medical Monitor or designee.** Patients should be closely monitored for potential toxicities. …

Rationale for Change:

To provide clarification on the used of prohibited concomitant medications for management of an AE and when TAK-659 could restart.

Change 30: Added that females cannot donate ova and males cannot donate sperm for 180 days after the last dose of study drug.

The primary change occurs in Section 8.6.1 Pregnancy and Contraception.

Amended text:	…Nonsterilized female patients of the reproductive age group and male patients should use effective methods of contraception throughout defined periods during and after study treatment as specified below: … **5) Female patients should not donate ova from the time of signing the informed consent through 180 days after the last dose of study drug.**

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

Rationale for Change:

For consistency with the ICF and other TAK-659 protocols noting restrictions for female donation of ova and male donation of sperm through 180 days after last dose of study drug.

Change 31: Added monitoring and prophylaxis procedures for cytomegalovirus (CMV).

The primary change occurs in Section 8.7.1 Prophylaxis Against Infections.

Amended text:

8.7.1.1 Cytomegalovirus Monitoring and Prophylaxis

~~Patients with advanced hematologic malignancies may have 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 with the underlying disease. Lymphopenia can be associated with reactivation of herpes zoster, cytomegalovirus, herpes simplex, and other viruses. Antiviral therapy such as acyclovir, ganciclovir, valacyclovir, or other antiviral agents may be initiated as clinically indicated. Testing and monitoring for cytomegalovirus replication and prophylactic or preemptive therapy to asymptomatic patients, if indicated, should follow the institutional standard practice.~~

At screening, all patients must have CMV serology and quantitative polymerase chain reaction (PCR) assay performed. CMV monitoring with a quantitative PCR assay will be performed as specified in the Schedule of Events. If positive at baseline, CMV monitoring is advised once a week with a decrease to a monthly frequency as it becomes negative. Preemptive treatment should be initiated based on the local CMV copy number per institutional practice. Prophylactic treatment can be initiated per investigators' discretion based on the risk assessment (even if the CMV test is negative at baseline). Interruption of study drug is generally advised if the positive CMV test is accompanied by associated clinical symptoms or the copy number reaches a level that treatment is indicated per institutional standard or the CMV test remains positive despite the antiviral treatment for CMV. If the study drug is interrupted, it can be resumed only after the infection has resolved. CMV monitoring is advised for the duration of the study as described in Section 9.4.13.3 and in the Schedule of Events (Appendix A).

The following agents could be considered for prophylaxis or pre-emptive treatment against cytomegalovirus: ganciclovir (intravenous [IV]), valganciclovir (PO), foscarnet (IV), or cidofovir (IV). Duration of antiviral therapy generally is for at least 2 weeks until cytomegalovirus is no longer detected.

8.7.1.2 Prophylaxis for Pneumocystis jiroveci Pneumonia

Patients with lymphopenia may also be prone to developing infections, such as respiratory infections including pneumonia. Consider a diagnosis of opportunistic infection including *Pneumocystis jiroveci* pneumonia (PJP) in patients presenting with shortness of breath, cough, or fever. Prophylaxis for PJP must be initiated (either at baseline or during treatment) if at least 1 of the following is present:

…

Rationale for Change:

To be able to monitor CMV reactivation, which has frequently occurred across the TAK-659 program. Monitoring and prophylaxis procedure are added to prevent CMV disease.

Change 32: Added CMV tests to be done at screening and monitored throughout the study.

The primary change occurs in Section 9.4.13 Clinical Laboratory Evaluations.

Added text:

9.4.13.3 CMV Testing

Patients will be tested at screening for CMV. CMV will continue to be monitored throughout the study.

Tests at screening include CMV serology (immunoglobulin [Ig]G and IgM) and quantitative PCR for CMV. Quantitative PCR for CMV monitoring will be performed as specified in the Schedule of Events (Appendix A).

Rationale for Change:

To reflect the addition of CMV monitoring.

The following sections also contain this change:

- Schedule of Events (Appendix A)

Change 33: Removed the text describing central reading of radiographic images.

The primary change occurs in Section 9.4.15 Disease Assessment.

Amended text:

9.4.15.2 ~~DLBCL~~ Expansion Part

…

Response assessments should include radiographic imaging (CT and FDG-PET), evaluation of symptoms, and bone marrow aspirate/biopsy if appropriate. The FDG-PET imaging should be done minimally at Screening and at the end of Cycles 2, 6, and 12 if positive at baseline or clinically indicated. ~~Central collection of images at imaging time points by the sponsor or designee is required.~~

…

Rationale for Change:

To reflect the current plan for not performing central reading of the radiographic imaging.

Change 34: Revised the instructions for performing CT scans for disease assessment in the expansion part.

The primary change occurs in Section 9.4.15 Disease Assessment.

Amended text:

9.4.15.2.1 CT Scans

CT scans of the chest, abdomen, and pelvis (neck should be included, if appropriate) will be performed to assess baseline disease at Screening and to assess disease response 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~~**or** oral contrast **(**unless **medically** 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**/oral** 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**/oral** contrast to avoid compromising PET results.

Rationale for Change:

CT with oral contrast may be more appropriate than CT with IV contrast, depending on location of the lesion.

CCI

[redacted]

CCI

Change 36; Added and reorganized tables indicating the PK, ECG, and pharmacodynamic assessment schedules for the dose escalation part and the expansion part in Appendix A.

The primary change occurs in Appendix A. References to these tables are revised throughout the protocol accordingly.

Description of change:

- Two new tables were added to show the PK, ECG and pharmacodynamic assessment schedules for patients who are on Dosing Schedule B (7 days on/7 days off intermittent dosing). These tables are now placed in the following order:
  - Table A: Dose Escalation Part (Dosing Schedule A) PK, ECG, and Pharmacodynamic Assessment Schedule

- Table B: Dose Escalation Part (Dosing Schedule B) PK, ECG, and Pharmacodynamic Assessment Schedule
- Table C: Expansion Part (Dosing Schedule A) Sparse PK and Pharmacodynamic Assessments Schedule
- Table D: Expansion Part (Dosing Schedule B) Sparse PK and Pharmacodynamic Assessments Schedule

- Columns for the collection of PBMC were added.

Rationale for Change:

- To reflect the addition of the new intermittent dosing schedule.
- To reflect the addition of a new pharmacodynamic assessment.

The following sections also contain this change:

- Section 9.4.17 PK Measurements
- Section 9.9 Study Compliance

Change 37: Added description on the blood sample collection time points for PK for subjects on the new Dosing Schedule B (7 days on/7 days off intermittent dosing).

The primary change occurs in Section 9.4.17 PK Measurements and Section 13.1.5 Pharmacodynamic Analysis and PK/Pharmacodynamic Analysis .

Amended text:

9.4.17.1 PK Measurements for the Dose Escalation Part

In all dose escalation patients, blood samples for determination of the plasma concentrations of TAK-659 will be collected ~~in Cycle 1 on Days 1, 2, 8, 15, 16, and 22~~ at the times indicated in Appendix A, Table A **(Dosing Schedule A) or Table B (Dosing Schedule B).**

To determine urine concentrations of TAK-659, a spot urine collection will be obtained predose on Cycle 1 Day 1, and a urine collection will be obtained in the clinic **either** on Cycle 1 Day 15 **(for patients on Dosing Schedule A) or Cycle 1 Day 7 (for patients on Dosing Schedule B)** at 0 to 8 hours postdose. …

…

The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on PK sample collection days (Cycle 1 Days 1, 2, 8, 15, 16, and 22~~).~~ **[Dosing Schedule A] or Cycle 1 Days 1, 2, 7, 8, 15 and 22 [Dosing Schedule B]).** …

9.4.17.2 PK Measurements for the ~~DLBCL~~ Expansion Part

For ~~DLBCL~~ expansion patients (except for a potential subset of Japanese patients), blood samples for determination of TAK-659 plasma concentrations will be collected

during Cycles 1 through 4 according to a sparse sampling schedule at the times indicated in Appendix A, ~~Table B.~~ **Table C (Dosing Schedule A) or Table D (Dosing Schedule B).** Specifically, blood samples will be collected on Days 1, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2 through 4~~.~~ **(for patients on Dosing Schedule A) or Days 1, 7 and 21 of Cycle 1 and on Day 7 of Cycles 2 through 4 (for patients on Dosing Schedule B).** No urine PK samples will be collected in expansion patients designated for sparse PK sampling. If fewer than 6 Japanese patients are dosed at the RP2D in the dose escalation part, additional intensive PK samples will be collected during Cycle 1 in a subset of Japanese patients in the ~~DLBCL~~ expansion part. For this subset, additional blood samples and 2 urine samples should be collected as specified in Appendix A, Table A and **Table B**.

…

CCI

[redacted]

Rationale for Change:

To reflect the addition of the new intermittent dosing schedule.

Change 38: Added a new section for blood sample collection for assessment of the pharmacodynamic effects of TAK-659 on circulating immune cells.

The primary change occurs in Section 9.4.18 Pharmacodynamic Measurements.

Amended text:

9.4.18.1 Serum Samples for Pharmacodynamic Measurements for Cytokines/Chemokines/Serum Proteins

Serum samples will be collected from all patients ~~for pharmacodynamic evaluation~~ as indicated in the Schedule of Events (Appendix A, Table A, Table B, **Table C and Table D**), and the cytokines/chemokines/**proteins** 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.

9.4.18.2 Blood Samples for Pharmacodynamic Measurements for Circulating

Immune Cells by Flow Cytometry

Blood samples will be collected from all patients as indicated in the Schedule of Events (Appendix A, Table A, Table B, Table C and Table D). Peripheral blood mononuclear cells (PBMCs) isolated and cyropreserved to evaluate the response of circulating immune cells to TAK-659 treatment during the different treatment regimens. Blood will only be collected during Cycle 1 for immunophenotyping.

Rationale for Change:

To reflect the addition of a new pharmacodynamic assessment.

The following sections also contain this change:

- Schedule of Events (Appendix A)

Change 39: Pregnancy was added to the reasons for discontinuation of treatment with study drug.

The primary change occurs in Section 9.6 Completion of Study.

Amended text:

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

…

- Initiation of hematopoietic stem cell transplant.
- **Pregnancy.**
- Study terminated by sponsor.

…

Rationale for Change:

For consistency with other TAK-659 protocols.

Change 40: Pregnancy was added to the reasons for withdrawal of patients from study.

The primary change occurs in Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement.

Amended text:

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

…

- Initiation of hematopoietic stem cell transplant.
- **Pregnancy.**
- Study terminated by sponsor.

…

Rationale for Change:

For consistency with other TAK-659 protocols.

Change 41: Revised the posttreatment follow-up assessments section.

The primary change occurs in Section 9.10 Posttreatment Follow-up Assessments (PFS) (Expansion Part Only).

Amended text:

Patients enrolled in the ~~DLBCL~~ expansion part who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visits should be conducted at the study site every 2 months for up to 6 months after the last dose of study drug or until PD, whichever occurs first.

~~Survivor information and death details 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, the start of another anticancer therapy for the disease under study will be collected.~~

If a patient has transitioned to either autologous 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.

…

Rationale for Change:

Removed description on the collection of survivor information, since overall survival data is not collected in this study.

Change 42: Revised the PK analysis section.

The primary change occurs in Section 13.1.4 PK Analysis.

Amended text:

The plasma and urine concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods. For patients who undergo intensive **or sparse** PK sampling in either dose escalation or ~~DLBCL~~ expansion, plasma TAK-659 concentrations ~~obtained from Cycle 1~~ will be summarized by descriptive statistics according to nominal (scheduled) time postdose ~~(except for 2-4 hr postdose on Day 22)~~, dose level, ~~and~~ day **and cycle**. ~~For DLBCL expansion patients undergoing sparse PK sampling, only plasma concentrations from Cycle 1 predose samples will be summarized by day (plasma concentrations obtained from Cycle 1, 2-4 hr postdose samples and from Cycles 2 through 4 predose samples will be listed but not summarized).~~ For patients who undergo intensive PK sampling in either dose escalation or ~~DLBCL~~ expansion, mean and individual plasma TAK-659 concentration data from Cycle 1will be plotted over time and grouped according to dose level and day, including a graphical presentation of mean and individual concentration-time data in the Japanese patients at the RP2D who undergo intensive PK assessments. All plasma and urine concentration data will be listed by patient,

dose level, dosing cycle and day, and nominal and actual time point.

13.1.4.1 Noncompartmental PK Analysis

Plasma and urine PK parameters **for patients with intensive PK sampling** will be estimated in the PK analysis set using noncompartmental methods. The following PK parameters will be determined as permitted by available data: C_{max}, T_{max}, AUC_{τ}, CL/F, C_{trough}, Rac, PTR, CL_R, and CL_R as a percentage of CL/F.

…

Rationale for Change:

To extend the summary of PK concentration in every cycle of the expansion phase, and to clarify that the noncompartmental PK analysis is only applicable for patients with intensive PK sampling.

CCI

[redacted]

Change 44: Revised Table 13.a (Probabilities of Observing the Minimum Number of Responders Given True Response Rates, Assuming a Total of 12 Response-Evaluable Patients).

The primary change occurs in Section 13.3 Determination of Sample Size.

Description of change: The probability of observing a certain number of responders were originally estimated on the basis of the true TAK-659 response rate as being 20%, 30%, 40% and 50%, but these numbers were re-estimated using true TAK-659 response rates of 20%, 40%, 60% and 80%.

Rationale for Change:

To reflect the new target tumor types (FL and MZL) in the expansion part.

Change 45: Updated the protocol deviations section.

The primary change occurs in Section 14.2 Protocol Deviations.

Amended text:

…

The site should document all protocol deviations in the subject'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 subject, or confound interpretation of **the** 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.~~

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

…

Rationale for Change:

For consistency with the latest protocol template.

Change 46: Updated the IRB and/or IEC approval section.

The primary change occurs in Section 15.1 IRB and/or IEC Approval.

Amended text:

… 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. **If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment.** The sponsor or its designee will notify site once the sponsor or its designee has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor or its designee has received permission from **the** competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

…

Rationale for Change:

For consistency with the latest protocol template.

Change 47: Revised the list of references.

The primary change occurs in 16.0 REFERENCES.

Description of change: Added new references and rearranged the numbering of the references. Cross-references are also revised throughout the protocol for consistency.

Rationale for Change:

To reflect the addition of new references.

Change 48: Revised to allow predose ECG to be performed outside the 1 hour window before dosing.

The primary change occurs in the Schedule of Events (Appendix A), Table A. The new Table B has been prepared with this change incorporated.

Description of change: Added a new footnote (b) to the Schedule of Events, Table A, to indicate this rule.

Rationale for Change:

To allow flexibility to the predose ECG timing for study visits when multiple examination procedures coincide. As long as the predose ECG is performed before dosing, the timing is of little clinical significance.

CCI [redacted]

The primary change occurs in the Schedule of Events (Appendix A), Table A. The new Table B has been prepared with this change incorporated.

Description of change:
- Added a note in the cells for postdose pharmacodynamic sample collection in Schedule of Events, Table A (and the new Table B), to indicate this requirement.
- In Schedule of Events, Table C (and the new Table D), the following revision has been made:
  2 ~~to~~**or** 4 hours post dose

Rationale for Change:

To clarify the timing of blood collection for the original and additional dosing schedules.

Change 50: Updated the Schedule of Events.

The primary change occurs in Schedule of Events (Appendix A), including Table A, Table B, Table C and Table D.

Description of change:

For both the dose escalation part and expansion part:

- Revised texts for TAK-659 administration to reflect the new dosing schedule.
- Added a new row for CMV testing.
- Added a new row for the collection of blood samples for flowcytometry.
- Added new columns according to the new sample collection time points for PK.

Dose escalation part only:

- Revised texts in several rows (12-lead ECG, blood samples for PK, urine samples for PK, serum samples for pharmacodynamics) to refer to Table A for subjects on Dosing Schedule A and to refer to the new Table B for subjects on Dosing Schedule B.

Expansion part only:

- Revised texts in several rows (blood samples for sparse PK and blood samples for intensive PK) to refer to Table A for subjects on Dosing Schedule A and to refer to the new Table B for subjects on Dosing Schedule B.

Rationale for Change:

For consistency with the revisions/updates made to the other sections of this protocol amendment.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	11-Dec-2018 01:20 UTC
	Clinical Pharmacology Approval	11-Dec-2018 01:42 UTC
	Clinical Approval	11-Dec-2018 01:48 UTC
	Biostatistics Approval	11-Dec-2018 14:51 UTC